

EXPERT REPORT, ANNA LEMBKE, M.D.

April 16, 2021

RELATING TO

The County of Lake, Ohio vs. CVS Health Corporation; CVS Indiana LLC; CVS RX Services, Inc.; CVS TN Distribution LLC; CVS Pharmacy, Inc.; Omnicare Distribution Center LLC; Ohio CVS Stores, LLC; Walgreen Co.; Walgreens Boots Alliance, Inc.; Walgreen Eastern Co., Inc.; Rite Aid Corp.; Rite Aid HDQTRS. Corp.; Eckerd Corporation D/B/A Rite Aid Liverpool Distribution Center; Rite Aid of Ohio, Inc.; Rite Aid of Maryland, Inc.; HBC Service Company; Giant Eagle, Inc.; Walmart Inc. F/K/A Wal-Mart Stores Inc.; Wal-Mart Stores East LP; WSE Management, LLC; WSE Investment LLC; and Wal-Mart Stores East, Inc.

The document relates to: Case No. 18-op-45032

The County of Trumbull, Ohio vs. CVS Health Corporation; CVS Indiana LLC; CVS RX Services, Inc.; CVS TN Distribution LLC; CVS Pharmacy, Inc.; Ohio CVS Stores LLC; Walgreen Co.; Walgreens Boots Alliance, Inc.; Walgreen Eastern Co., Inc.; Rite Aid Corp.; Rite Aid HDQTRS. Corp.; Eckerd Corporation D/B/A Rite Aid Liverpool Distribution Center; Rite Aid of Ohio, Inc.; Rite Aid of Maryland Inc.; HBC Service Company; Giant Eagle Inc.; Walmart Inc. F/K/A Wal-Mart Stores Inc. ' Wal-Mart Stores East LP; WSE Management LLC; WSE Investments LLC; and Wal-Mart Stores, Inc.

This document relates to Case No. 18-op-45079

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A. Background and Qualification

1. I am Professor, Chief of the Addiction Medicine Dual Diagnosis Clinic, Medical Director of Addiction Medicine, and Program Director of the Addiction Medicine Fellowship, in the Department of Psychiatry and Behavioral Sciences at Stanford University School of Medicine. Since 2016, I also hold a Courtesy Appointment in the Stanford University Department of Anesthesiology and Pain Medicine. I began my faculty career at Stanford in 2003. A true copy of my current CV is attached to this Report as Exhibit A.

2. I received my undergraduate degree in Humanities from Yale University in 1989, and my medical degree from Stanford University in 1995, where I also completed a partial residency in Pathology (1997) and a full residency in Psychiatry (2000), as well as a Fellowship in Mood Disorders, Department of Psychiatry and Behavioral Sciences (2002).

3. I have been licensed to practice medicine in the State of California from 1995 to the present. I received the DEA-X waiver to prescribe buprenorphine products in 2013. I am a diplomate of the American Board of Psychiatry and Neurology (2003; recertified, 2013), and a diplomate of the American Board of Addiction Medicine (2013).

4. From 2001 to the present, I have taught medical students, residents, and fellows at Stanford University School of Medicine, on a diversity of topics related to psychiatry, addiction, and pain. For example, from 2004 to the present, I have given annual lectures on addiction medicine within the Practice of Medicine (POM) series for Stanford medical students, including topics such as the neurobiology of addiction, how doctors should intervene when they detect substance use problems, and how to have difficult conversations with patients on the topic of substance use, misuse, overuse, and addiction.

5. I received the Stanford Award for Excellence in Academic Teaching, Department of Psychiatry, in 2014, and again in 2018.

6. In 2013 I founded and became the Training/Program Director for Stanford's Addiction Medicine Fellowship, a post-graduate sub-specialty training year in the treatment of addiction for any medical graduate of a U.S. or Canadian medical school and ACGME-accredited residency. In 2020 I was awarded the ASAM Training Directors Award "for outstanding training in the evaluation, treatment, research and teaching of substance use disorders."

7. As a full time faculty at the Stanford University School of Medicine, I regularly treat patients with addiction to opioids and other substances. For the last 15 years, my clinical practice has included a significant proportion of patients taking prescription opioids for pain relief, for whom such drugs have resulted in misuse, dependence, and addiction. As an integral part of my practice, I work with these patients to develop treatment plans that will address their pain while making appropriate efforts to reduce (taper) or eliminate use of opioids, and/or treat their opioid addiction. Such plans can include non-opioid medications for pain, as well as alternative, non-pharmaceutical modalities, and counseling, with a dual focus on treating the underlying painful condition and the substance use disorder. I frequently collaborate with pain

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and primary care colleagues concerning populations with chronic pain and substance use disorders.

8. In 2015, I received the Stanford Chairman's Award for Clinical Innovation for developing inpatient and outpatient clinical services dedicated to helping people with substance use problems.

9. In January 2015, I was appointed by Governor Jerry Brown to the Research Advisory Panel of California. I served on the Panel until 2017. I, along with the other Panel members, was tasked with assessing the safety of clinical trials to be conducted in the state of California using controlled substances, such as opioids. In this capacity, I applied my knowledge and experience to the review of study designs and protocols, and I made recommendations for procedures to protect patients in these trials, including, in particular, protection from potential harmful effects of opioids.

10. From 2015 to 2019, I served on the Board of the California Society of Addiction Medicine (CSAM). I have been a member of CSAM, and the American Society of Addiction Medicine (ASAM), since 2011.

11. In 2015-2016 I chaired the Planning Committee for the California Society of Addiction Medicine (CSAM) Annual Addiction Medicine Conference.

12. In 2016, I became president of the Addiction Medicine Fellowship Directors Association (AMFDA).

13. In 2016, I led a program funded by the Stanford Center for Continuing Medical Education (SCCME), titled, "Tapering Patients Off of Chronic Opioid Therapy."¹

14. Since 2016, I have chaired the Addiction Medicine Task Force, Stanford University School of Medicine. The goal of the Task Force is to re-evaluate and re-create the medical school curriculum on addiction and safe prescribing of addictive substances. I have served as MedScholar Advisor on the topic of *Developing the Addiction Curriculum at Stanford*, Stanford University School of Medicine. The new medical school curriculum we have created includes didactics on the neurobiology of addiction, the treatment of addiction, the management of opioid prescribing in the setting of chronic pain, and the history and origins of the opioid epidemic.

15. In 2019, the Stanford Center for Health Education asked me to lead and design an online course on addiction for Stanford learners all over the world. This course is called "The Psychology of Addiction and Recovery" and explores concepts of addiction through time, risk factors for addiction, and treatments for addiction including biological, psychological and public policy approaches. The course has been available since August 2020.

¹ *How to Taper Patients Off of Chronic Opioid Therapy*, Stanford University School of Medicine, <https://med.stanford.edu/cme/courses/online/opioid-taper.html>. Chronic pain is frequently considered to be pain that lasts longer than 3 months. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA* 2016;15(15):1624–1645, at p. 1625.

16. I am the author of a book on the prescription drug epidemic: *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop* (Johns Hopkins University Press, 2016).² My book was highlighted in the *New York Times* as one of the top five books to read to understand the opioid epidemic.³

17. I have published over 100 peer-reviewed articles, chapters, and commentaries, which have appeared in the *New England Journal of Medicine*, *Journal of the American Medical Association*, *Pain Medicine*, *Journal of General Internal Medicine*, *Addiction*, and other peer reviewed journals. Many of these publications address the diagnosis and treatment of addiction, as well as the treatment of pain. I have also published articles on the importance of teaching addiction medicine in medical school, residency, and fellowship.

18. In 2016, I co-authored a peer-reviewed article, “Weighing the Risks and Benefits of Chronic Opioid Therapy,” which addressed issues of opioid misuse and addiction, risk assessment and mitigation, patient education, tapering to reduce or end opioid exposure, tolerance, dependence, and risks of overdose.⁴ *American Family Physician* is among the most read family physician peer reviewed journals. The readership includes 32,000 medical students and over 3,700 nurse practitioner and physician assistant subscribers.

19. In 2016, I co-authored a Research Letter in *JAMA Internal Medicine* that examined Medicare data on opioid drug prescription patterns. Our analysis concluded that opioid prescribing is “a widespread practice relatively indifferent to individual physicians, specialty or region. High-volume prescribers are not alone responsible for the high national volume of opioid prescriptions. Efforts to curtail national opioid overprescribing must address a broad swath of prescribers to be effective.”⁵ This article has been cited 130 times in the 4 years since its publication,⁶ and demonstrates that the epidemic of opioid drug misuse and addiction is attributable to many prescribers, including but not limited to high-frequency prescribers, who are sometimes referred to as “pill mills.”

20. In 2016, I co-authored a Research Letter in *JAMA Psychiatry* on the high exposure to opioids among Medicare patients, the growing incidence of opioid use disorder in

² Lembke, Anna. *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why Its so Hard to Stop*. Johns Hopkins University Press, 2016.

³ Abigail Zuger, *A Doctor's Guide to What to Read on the Opioid Crisis*, N.Y. Times (Dec. 17, 2018)

⁴ Lembke A, Humphreys K, Newmark J. Weighing the risks and benefits of chronic opioid therapy. *Am Fam Physician*. 2016; 93(12):982-990.

⁵ Chen JH, Humphreys K, Shah NH, Lembke A. Distribution of opioids by different types of medicare prescribers. *JAMA Intern Med*. December 2015:1-3. <http://dx.doi.org/10.1001/jamainternmed.2015.6662>, at pp. 260-261.

⁶ “Distribution of opioids by different types of medicare prescribers” Google Scholar Results https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=Lembke+Distribution+of+opioids+by+different+type+s+of+medicare+prescribers&btnG= (last accessed January 22, 2021)

this population, and the lack of buprenorphine prescribers in this population, noting the gap between the need for treatment and access to that treatment.⁷

21. In 2018, I co-authored two articles in peer-reviewed pain journals on pain management of patients with chronic pain and opioid use disorder.^{8,9}

22. In 2019, I co-authored two articles in peer-reviewed journals on how to transition hospitalized patients with opioid use disorder onto opioid agonist therapy while still managing their pain conditions.¹⁰ Opioid agonist therapy refers here to buprenorphine, an opioid used to treat severe opioid use disorder, but which can be difficult to initiate in patients already on opioids due to its unique chemical properties (high binding affinity).

23. In 2018 and 2020, I co-authored two articles in peer-reviewed journals on the risks of opioid and benzodiazepine co-prescribing.¹¹

24. I have devoted a significant portion of my professional career to the development of a patient-centered protocol to reduce or discontinue prescription opioid use among individuals with opioid dependence and chronic pain, called the BRAVO Protocol. This academic detailing material, free of commercial bias, includes but is not limited to infographic handouts, a website platform (<https://www.oregonpainguidance.org/guideline/tapering/>) and a free Stanford-supported, online, continuing medical education course (<https://med.stanford.edu/cme/courses/online/opioid-taper.html>), enduring web-based material (<https://www.oregonpainguidance.org/guideline/tapering/>), and peer-reviewed publications. The BRAVO Protocol has been widely disseminated and recognized by leading authorities. In 2019, the United States Department of Health and Human Services (HHS) was preparing to issue the HHS Guide for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-Term Opioid Analgesics. Authors of the HHS Guidelines asked for permission to include a decision-making “flow chart” from the BRAVO Protocol and a previously published article that I co-authored in the *Annals of Internal Medicine* in August 2019. That permission was granted, and the HHS Guidelines included an adaptation of our published decision tree, providing

⁷ Lembke A, Chen JH. Use of opioid agonist therapy for medicare patients in 2013. *JAMA Psychiatry*. 2016;73(9). doi:10.1001/jamapsychiatry.2016.1390.

⁸ Harrison TK, Kornfeld H, Aggarwal AK, Lembke A. Perioperative Considerations for the Patient with Opioid Use Disorder on Buprenorphine, Methadone, or Naltrexone Maintenance Therapy. *Anesthesiol Clin*. 2018;36(3):345-359. doi:10.1016/j.anclin.2018.04.002.

⁹ Lembke A, Ottestad E, Schmiesing C. Patients Maintained on Buprenorphine for Opioid Use Disorder Should Continue Buprenorphine Through the Perioperative Period. *Pain Med*. 2018;(February):1-4. doi:10.1093/pm/pny019.

¹⁰ Raheemullah, A., Lembke, A. Initiating Opioid Agonist Treatment for Opioid Use Disorder in the Inpatient Setting: A Teachable Moment, *JAMA Internal Medicine*, 2019; 179(3):427-428. Raheemullah, A., Lembke, A. Buprenorphine Induction Without Opioid Withdrawal: A Case Series of 15 Opioid-Dependent Inpatients Induced on Buprenorphine Using Microdoses of Transdermal Buprenorphine. *American Journal of Therapeutics*, 2019; 0:1-7.

¹¹ Lembke, A., Papac, J., Humphreys, K. Our Other Prescription Drug Problem, *N Engl J Med* 2018; 378(8):693-695; Azad, Lembke, A. et al, Patterns of Opioid and Benzodiazepine Use in Opioid-Naïve Patients with Newly Diagnosed Low Back and Lower Extremity Pain, *J Gen Intern Med*, 2019, 35(1):291-297. doi: 10.1007/s11606-019-05549-8.

recommendations on how and when to taper patients from long-term opioid use.¹² On October 10, 2019, the *Journal of the American Medical Association (JAMA)* published a commentary about the HHS Guidelines, authored by officials of the United States Centers for Disease Control and the National Institute on Drug Abuse.¹³ In addition, in January 2020, *American Family Physician* published my article, “Tapering Long-Term Opioid Therapy,” which was offered to professionals for 6 hours of Continuing Medical Education (CME) credit, further documenting the acceptance of my work in this area.¹⁴ The BRAVO Protocol material and accompanying free Stanford CME course have been adopted in several states as part of CME on safe opioid prescribing. The BRAVO Protocol has been used as a guiding framework for opioid tapering in clinics across the country (see Appendix IV).¹⁵

25. I have testified before the United States House of Representatives on the opioid epidemic and ways to mitigate harms caused by that epidemic, and I have presented at numerous conferences before governmental, professional, academic and lay audiences on related topics.

26. Since the publication of my book, *Drug Dealer, MD*, I have been invited to make presentations to doctors, legislators, and the public, regarding the causes of the opioid epidemic and how we can combat it. A significant portion of my work in this area consists of describing the false and misleading messages promoted by the Pharmaceutical Opioid Industry as detailed in this Report, including but not limited to unsupported claims of long-term efficacy for chronic pain, false representations of the risk of addiction, downplaying the risks of dependence and withdrawal, and misinforming doctors about the extent to which opioid doses could safely be increased. As to all of these subjects, it has been my experience that audiences of professionals and lay persons alike continue to be misled by the decades-long campaign of misinformation promoted through the Industry's marketing of opioids. “Academic detailing” is the process of providing accurate information to medical providers about the risks and benefits of a drug, to balance and re-educate after exposure to one-sided and inaccurate messaging from the detailers who have conveyed Industry messages to those providers over extended periods of time. As noted by the Report of the Association of Schools and Programs of Public Health (ASPPH), issued in November 2019, there is a need for “*extensive academic detailing and counter-detailing on opioids* to correct the inaccurate and misleading claims previously made by the companies that manufacture those drugs, messages that continue to confuse or mislead some

¹² Chou, *et al.*, Rethinking Opioid Dose Tapering, Prescription Opioid Dependence, and Indications for Buprenorphine, *Ann Intern Med.* 2019; 171(6):427-429. As discussed in this Report, it is essential to patients' well-being that proper, patient-centered methods of tapering are followed, to reduce or eliminate opioid use without imposing unnecessary risks associated with rapid or formulaic discontinuation of these drugs.

¹³ Dowell, *et al.*, Patient-Centered Reduction or Discontinuation of Long-Term Opioid Analgesics. *JAMA.* 2019;322(19):1855-1856. doi:10.1001/jama.2019.16409; Chou, *et al.*, Rethinking Opioid Dose Tapering, Prescription Opioid Dependence, and Indications for Buprenorphine, *Ann Intern Med.* 2019;171(6):427-429. doi: 10.7326/M19-1488.; United States Department of Health and Human Services. HHS Guide for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-term Opioid Analgesics. (October 2019); https://www.hhs.gov/opioids/sites/default/files/2019-10/Dosage_Reduction_Discontinuation.pdf, at p. 3.

¹⁴ Lembke A., Tapering Long-Term Opioid Therapy. *Am Fam Physician* 2020; 101(1):49-52.

¹⁵ See also Perez, M. “Tapering Long-Term Opioids Can Be Both Patient-Centered and Evidence-Based.” Washington Medical Commission, (2021). <https://wmc.wa.gov/sites/default/files/public/Newsletter/opioids.pdf>, for example of successful use of BRAVO protocol.

patients and prescribers.”¹⁶ I began and performed my work in academic detailing before any connection or thought of involvement in litigation, and I continue in this role to counter the false and misleading marketing messages of the Pharmaceutical Opioid Industry.

27. I have substantial experience in the study and teaching on the marketing of opioids, the impacts of such marketing on prescribing habits of physicians, and the effects of market-driven prescribing as a cause of the ongoing opioid epidemic. I have taught extensively at Stanford University and other institutions of higher learning on the ways in which the Pharmaceutical Opioid Industry marketed prescription opioids as both more effective and less addictive than they really are. My lectures have included coverage of overt, aggressive marketing tactics (such as detailing by company sales representatives, coupons for free or discounted opioids, and free lunches or dinners provided to doctors), as well as the Industry’s covert partnerships with, and financial support for, organizations with significant influence on the practice of medicine (e.g., The Joint Commission, The Federation of State Medical Boards, and professional medical societies such as the American Academy of Pain Medicine and the American Pain Society). My lectures have also included discussion of my firsthand experience of these marketing tactics, as well as their continuing impact on several generations of doctors. I have lectured on the Industry’s extensive publications in the peer-reviewed medical literature, explaining that these tactics influence physicians’ opioid prescribing practices. I am frequently asked to peer-review articles for publication in medical journals regarding the influence of the pharmaceutical industry’s marketing on prescribing practices. I have given lectures on these subjects to Stanford undergraduates, Stanford business, law, public health, and medical students, among others. I have also spoken on these topics widely outside of Stanford. In the fall of 2020, I taught at Duke University’s Global Health Institute on the subject of “market driven epidemics.”

28. Since the time of my previous report in this litigation, I have conducted further research concerning the role of pharmacies in the opioid epidemic, and I have also reviewed documents provided by counsel on that subject. These documents and their significance are discussed in Opinion 6, below. Throughout my career I have interacted with pharmacies and pharmacists thousands of times. On any given clinic day I will have interactions with multiple pharmacies and pharmacists pertaining to prescriptions I have written or others have written for patients in my care. The nature of these interactions with pharmacists can be accurately described as a partnership between professionals, with the overarching goal being the safety and best interests of our patients. Due to my role as a frequent prescriber of scheduled pharmaceuticals, I am familiar with the Controlled Substances Act, which includes obligations to prevent unauthorized or illegitimate prescriptions of these potentially dangerous drugs, and to identify and investigate “red flags” which refers to any signs or indications that a particular prescription may be outside of the boundaries of a legitimate medical purpose. I am also aware that “The responsibility for the proper prescribing and dispensing of controlled substances is upon the prescribing practitioner, but a corresponding responsibility rests with the pharmacist who fills the prescription.”¹⁷

¹⁶ Association of Schools & Programs of Public Health (ASPPH) Report, “Bringing Science to Bear on Opioids,” 11/01/2019, https://aspph-wp-production.s3.us-east-1.amazonaws.com/wp-content/uploads/2019/09/ASPPH.Opioids.FINAL_11.01.20191.pdf, at p. 21.

¹⁷ Purpose of issue of prescription, 21 C.F.R. §1306.04(a)

29. In forming the opinions expressed in this Report, I have relied on my medical training, more than twenty years of clinical experience, and my own research on opioid prescribing. My research began circa 2001 and has been multimodal. I have done qualitative interviews with patients, providers, and others in the health care field on questions related to opioid prescribing. I have followed and analyzed the medical literature using PubMed and other academic search engines, along with different combinations of key words such as “pain, opioids, treatment, randomized clinical trials, open label trials, effectiveness, adverse effects, prescribing, addiction, dependence, overdose, etc. ...” I have compiled statistics published by the CDC and other government agencies. I have, in collaboration with colleagues, analyzed opioid prescribing databases such as Medicare Part D.^{18,19} As a regular and ongoing part of my practice, I conduct literature searches of research on the subjects of addiction and pain treatment, which is essential to my work with my patients. Indeed, given the large and increasing role of opioid drugs in addiction, the fields of addiction and pain medicine are inevitably intertwined, such that it is essential to my practice to remain aware of the state of scientific inquiry in both fields. Specifically for this Report, I have considered the materials listed in Exhibit B, attached. I hold the opinions stated in this Report to a reasonable degree of scientific certainty.

30. Attached as Exhibit A is a copy of my current curriculum vitae and a list of all publications authored by me in the past 10 years.

31. Attached as Exhibit B is a list of data or other information considered by me in forming the opinions expressed herein.

32. Attached as Exhibit C is a statement of my compensation for services performed in this case.

33. Attached as Exhibit D is a list of all cases in which I have testified as an expert at trial or by deposition during the past four years.

B. Opinions

For the reasons set forth in detail in this Report, I hold the following opinions:

1. The addictive nature of medicinal opioids has been known for centuries. The Pharmaceutical Opioid Industry’s²⁰ misrepresentations of the safety and efficacy of prescription opioids reversed a century of appropriate restrictions on the use of these dangerous drugs, and substantially contributed to the current opioid epidemic.

2. Addiction is a chronic, relapsing and remitting disease with a behavioral component, characterized by neuroadaptive brain changes resulting from exposure to addictive drugs. Every human being has the potential to become addicted. Some are more vulnerable than others. Risks for becoming addicted include genetic,

¹⁸ Chen *et. al.*, “Distribution of Opioids,” fn. 5, above, at p. 259.

¹⁹ Lembke, *et al.*, “Use of Opioid Agonist Therapy,” fn. 7, above, at p. 990.

²⁰ The term Pharmaceutical Opioid Industry includes the defendants in this case.

developmental, and environmental factors (nature, nurture, and neighborhood). One of the biggest risk factors for addiction is simple access to addictive drugs. When supply of an addictive drug is increased, more people become addicted to and suffer the harms of that drug. Prescription opioids are as addictive as heroin, and the Defendants' conduct in promoting increased supply and widespread access to prescription opioids has resulted in an epidemic of opioid addiction and overdose death.

3. Opioid prescribing began to increase in the 1980s and became prolific in the 1990s and the early part of the 21st century, representing a radical paradigm shift in the treatment of pain and creating more access to opioids across the United States.

4. The Pharmaceutical Opioid Industry contributed substantially to the paradigm shift in opioid prescribing through misleading messaging about the safety and efficacy of prescription opioids. The Industry disseminated these misleading messages through an aggressive sales force, key opinion leaders, medical school curricula, continuing medical education courses, clinical decision support tools, professional medical societies, patient advocacy groups, the Federation of State Medical Boards, and The Joint Commission.

5. Opioid distributors collaborated with opioid manufacturers and pharmacies to promote sales of opioid pain pills. Such coordinated efforts included programs to give away free samples of opioids, coupons to discount opioids, and promotion of specific opioid products under the guise of education. These activities increased the population of opioid users, dose and duration of opioid use, and the risk of opioid misuse, addiction, dependence, and death.

6. Pharmacies leveraged their unique and pivotal position in the opioid supply chain to contribute to the unprecedented and unchecked flow of opioid pain pills into the community. They alone had direct contact with opioid manufacturers and distributors upstream, and patients and prescribers downstream. Their coordinated efforts to "create demand" included advertising specific opioid products at the pharmacy counter, building opioid "Super Stores" to enhance unrestricted flow of opioid pain pills, spreading misinformation about the safety and efficacy of opioid pain pills, partnering with pro-opioid industry advocacy and lobbying organizations, ignoring "red flags" for misuse and diversion including concerns expressed by their own pharmacists, failing to provide pharmacists with sufficient time, resources, or incentives to investigate red flags, and failing to use or analyze their own dispensing data to assist pharmacies in identifying red flags. By increasing and assuring the supply of opioids and failing to provide effective controls against diversion, pharmacies contributed to opioid misuse, addiction, dependence, and death.

7. No reliable scientific evidence shows that long-term opioid therapy is effective for chronic non-cancer pain.

8. The Pharmaceutical Opioid Industry misrepresented that the risk of addiction to prescription opioids is "rare," or "less than 1%," when in fact prescription opioids are as addictive as heroin, and the risk of addiction is far higher than stated by

the Industry. The best, conservative data show an opioid addiction prevalence of 10-30% among chronic pain patients prescribed opioids.

9. Increased supply of prescription opioids contributed substantially to more individuals becoming addicted to opioids and transitioning from prescription opioids to illicit sources of opioids such as heroin and fentanyl (The Gateway Effect).

10. Increased supply of prescription opioids contributed substantially to more individuals, including newborns, becoming dependent on opioids, increasing their risk for opioid-related morbidity and mortality (The Dependence Effect).

11. Increased supply of prescription opioids contributed substantially to diversion of prescription opioids to individuals for whom they had not been prescribed (The Tsunami Effect).

12. The increased supply of prescription opioids through licit and illicit sources resulted in a prescription opioid epidemic in the United States. “Epidemic,” defined as an outbreak of disease that spreads quickly and affects many individuals at the same time, is the appropriate term to describe the increase in opioid related morbidity and mortality beginning in the 1990s and continuing to the present day.

13. There is no doubt a cause-and-effect relationship exists between the oversupply of prescription opioids and the opioid epidemic.

14. For the reasons explained, the Pharmaceutical Opioid Industry bears responsibility for the misrepresentation of safety and efficacy, the ubiquitous distribution of prescription opioids, and the unchecked dispensing of prescription opioids, which resulted in the ongoing epidemic. To the extent that other factors contributed, those conditions were exploited by the Industry to increase the extent of harm.

15. Ending the epidemic of opioid addiction, dependence, and death will require significant investment of resources. An effective strategy will be multifaceted and will accomplish the following: prevent new cases of addiction, dependence, and death (primary prevention), limit progression of harm (secondary prevention), and treat existing cases (treatment). These changes will require curbing opioid prescribing, re-educating patients and health care providers, creating de-prescribing clinics, promoting naloxone and other harm-reduction strategies, and building an enduring medical infrastructure to treat addiction.

C. Detailed Statement of Opinions

1. The addictive nature of medicinal opioids has been known for centuries. The Pharmaceutical Opioid Industry’s misrepresentations of the safety and efficacy of prescription opioids reversed a century of appropriate restrictions on the use of these dangerous drugs, and substantially contributed to the current opioid epidemic.

- a. Opioids are among the world's oldest known drugs. Use of opium from the poppy plant for medical, recreational, and religious purposes can be traced throughout history and across continents, beginning in the 4th century B.C.²¹
- b. In the 19th century, two major scientific advances in medicinal opioids had far-reaching consequences. In 1804, German pharmacist Friedrich Serturmer isolated morphine, an opioid alkaloid derived from opium and ten times as potent.²² In 1855, Alexander Wood invented the hypodermic syringe, making possible fast easy administration of morphine.²³
- c. It was assumed (wrongly) that opioids administered by a doctor using a hypodermic syringe would not be addictive. During the Civil War, opium, laudanum, and hypodermic morphine were used extensively to treat soldiers and Victorian housewives alike. Hypodermic morphine soon became the major driver of American's first opioid epidemic. Hundreds of reports in late nineteenth century medical journals detailed iatrogenic (physician-initiated) cases of morphine addiction. The risk of addiction increased in cases where doctors continued to administer hypodermic morphine over long periods of time for protracted illnesses.²⁴ The two most important risk factors were exposure to opioids and a history of chronic illness. In the 1870s and 1880s, America's per capita consumption of opioids tripled.²⁵
- d. In 1897, Bayer chemists, trying to find a less addictive form of morphine, synthesized heroin. Heroin was marketed by Bayer as a cough and cold remedy alongside Bayer Aspirin from 1898 to 1910.²⁶
- e. The opioid addiction epidemic of the late 19th and early 20th century (Narcomania) led to ever-stricter laws and regulations regarding the prescribing and dispensing of opioids in medical practice, beginning in the early 1900s with the Harrison Narcotic Act, which effectively made heroin illegal.²⁷
- f. As a result, the first several decades of the 1900s saw a steady decrease in the per capita consumption of medicinal opioids.²⁸ In 1888, 14.5 percent

²¹ Lembke A. Psychology of Addiction and Recovery. Lecture: History of Addiction (Stanford University, Fall/Winter 2020)

²² Meldrum ML. A capsule history of pain management. *JAMA*. 2003;290:2470-2475, at p. 2471

²³ Lembke, "Drug Dealer, MD", fn 2, above, at p. 42. *See also* Meldrum, "Capsule history", fn. 22, above, at p. 2471.

²⁴ Courtwright DT. "Dark Paradise: A History of Opiate Addiction in America". Harvard University Press; 2001, at pp. 46-47.

²⁵ *Id.* at pp. 2-3 and 62-63.

²⁶ Lembke, "Drug Dealer, MD", fn. 2, above, at pp. 30-31

²⁷ *Id.*, at footnote p. 57.

²⁸ Courtwright, "Dark Paradise", fn. 24, above, at p. 29

of prescriptions filled in Boston drug stores contained opioids. In 1908, the comparable figure for California was 3.6 percent.²⁹

- g. Subsequent opioid epidemics in the 1940s and 1970s were smaller scale heroin epidemics unrelated to medical prescribing.³⁰ They were targeted and quelled through a process of repatriating Vietnam war veterans, criminalization, and methadone maintenance treatment.³¹
- h. In 1970 the Controlled Substances Act (CSA) was passed, which serves as the cornerstone of today's drug scheduling system.³² Schedule I drugs were prohibited. Schedule II drugs, including medicinal opioids, were tightly regulated with dire warnings of addictive potential, no prescription refills, triplicate order forms for transfers, production quotas, enhanced storage security requirements, and preapproval for all imports and exports.³³
- i. Medical training and education throughout the 20th century, save for the last two decades, was filled with warnings about the addictive potential of medicinal opioids, even when prescribed to patients with severe pain and dire illness, but especially when used long term in the treatment of chronic pain. Physicians were urged to use opioids sparingly, for short duration, and only in cases of severe trauma and at the end of life.³⁴ For example, a peer-reviewed study published in 1954 concluded "Morphine is not the answer to chronic pain. Because of the development of tolerance to the analgesic effects of morphine, alleviation of pain becomes inadequate. Under such circumstances the physician, by gradually withdrawing narcotics, does not deprive the patient of any actual benefit but protects him and his family from the possible legal, social, or economic difficulties attendant on opiate addiction. The administration of morphine to a patient with chronic pain is a short-lived type of kindness. Long-term kindness would begin when opiates are withheld or withdrawn in favor of other therapeutic measures."³⁵
- j. The current opioid epidemic in the United States, occurring almost exactly 100 years after the first major opioid epidemic, was ushered in by the reversal of a century of prudential legislation and medical training. The result, since the 1990s, has been a prolonged period of opioid overprescribing with concomitant opioid addiction, dependence, and

²⁹ *Id.*, at p. 21.

³⁰ *Id.*, at p. 8.

³¹ *Id.*, at p. xii.

³² Lembke, "Drug, Dealer MD", fn. 2, above, at pp.57, 31 and 5.

³³ *Id.*, at p. 5.

³⁴ *Id.*, at pp. 56-57.

³⁵ Rayport M. Experience in the Management of Patients Medically Addicted to Narcotics. *JAMA - J Am Med Assoc.* 1954;156(7):684-691, at p. 690.

overdose death. When Defendants claim that knowledge of the addictive potential of medicinal opioids is new, they ignore 100 years of medical experience, knowledge, and legislation.³⁶ The addictive nature of medicinal opioids has been known for centuries.

2. Addiction is a chronic, relapsing and remitting disease with a behavioral component, characterized by neuroadaptive brain changes resulting from exposure to addictive drugs. Every human being has the potential to become addicted. Some are more vulnerable than others. Risks for becoming addicted include genetic, developmental, and environmental factors (nature, nurture, and neighborhood). One of the biggest risk factors for addiction is simple access to addictive drugs. When supply of an addictive drug is increased, more people become addicted to and suffer the harms of that drug. Prescription opioids are as addictive as heroin, and the Defendants' conduct in promoting increased supply and widespread access to prescription opioids has resulted in an epidemic of opioid addiction and overdose death.

- a. Addiction is the continued use of a substance despite harm to self and others and/or a desire to quit or cut back. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) uses the term “substance use disorder” to denote addiction. I use the terms “opioid addiction” and “opioid use disorder” interchangeably here.
- b. DSM-5 denotes 11 different criteria to diagnose opioid use disorder (OUD).³⁷ A short-hand way to remember these criteria is the “four C’s”: Control, Compulsion, Craving, and continued use despite Consequences.
 - i. Control refers to out-of-control use, for example using more than intended, or an inability to cut back use when necessary.
 - ii. Compulsion refers to mental preoccupation with using against a conscious desire to abstain.
 - iii. Craving refers to physiologic and/or mental states of wanting.
 - iv. Consequences refers to the social, legal, economic, interpersonal, and other problems that arise as a result of use, yet which still do not deter use.
- c. The physiological phenomena of tolerance and withdrawal are included in the DSM-5 criteria, but they are not required in order to make the diagnosis of opioid use disorder/addiction. In other words, tolerance and withdrawal are recognized as separate physiologic phenomena often seen in addiction, but not definitional for addiction. Further, under DSM-5, the

³⁶ Lembke, “Drug Dealer, MD”, fn. 2, above, at pp. 56-57

³⁷ *Diagnostic and Statistical Manual of Mental Disorders*. (DSM-5) Washington, DC: American Psychiatric Association; 2013 at p. 541.

criteria of tolerance and withdrawal do not count toward a diagnosis of addiction when a patient is prescribed opioids under the supervision of a doctor, making it more difficult to diagnose addiction to prescription opioids. As discussed later in this Report, Defendants influenced this definition by characterizing dependence as a benign condition entirely separate from addiction. In reality, dependence, withdrawal, and tolerance are closely linked to the disease of addiction, and from a neurobiological perspective, may be identical phenomena.

- d. The DSM-5 also recognizes that addiction is a spectrum disorder, divided into mild, moderate, and severe, based on the number of criteria met.³⁸
- e. The American Society of Addiction Medicine (ASAM) has defined addiction as follows: “Addiction is a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual’s life experiences. People with addiction use substances or engage in behaviors that become compulsive and often continue despite harmful consequences. Prevention efforts and treatment approaches for addiction are generally as successful as those for other chronic diseases”³⁹ This ASAM definition of addiction is consistent with but not identical to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). The ASAM definition does not single out any specific substance, highlighting the idea that all addictive drugs work on the same common brain pathway.
- f. From a neuroscience perspective, addiction is a disorder of the brain’s reward circuitry.⁴⁰
 - i. Opioids, in addition to binding the *mu*-pain receptors, also cause the release of the neurotransmitter dopamine. In order to accommodate the high amount of dopamine released, the brain adapts by downregulating its own endogenous dopamine and its

³⁸ *Id.* at pp. 541-542.

³⁹ American Society of Addiction Medicine (ASAM) Definition of Addiction. [https://www.asam.org/docs/default-source/quality-science/asam's-2019-definition-of-addiction-\(1\).pdf?sfvrsn=b8b64fc2_2](https://www.asam.org/docs/default-source/quality-science/asam's-2019-definition-of-addiction-(1).pdf?sfvrsn=b8b64fc2_2), (adopted September 15, 2019), at p. 2. Prior to 2019, ASAM defined addiction as follows: “Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors. Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one’s behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.” <https://www.asam.org/resources/definition-of-addiction>, at p. 1. (last accessed June 20, 2018)

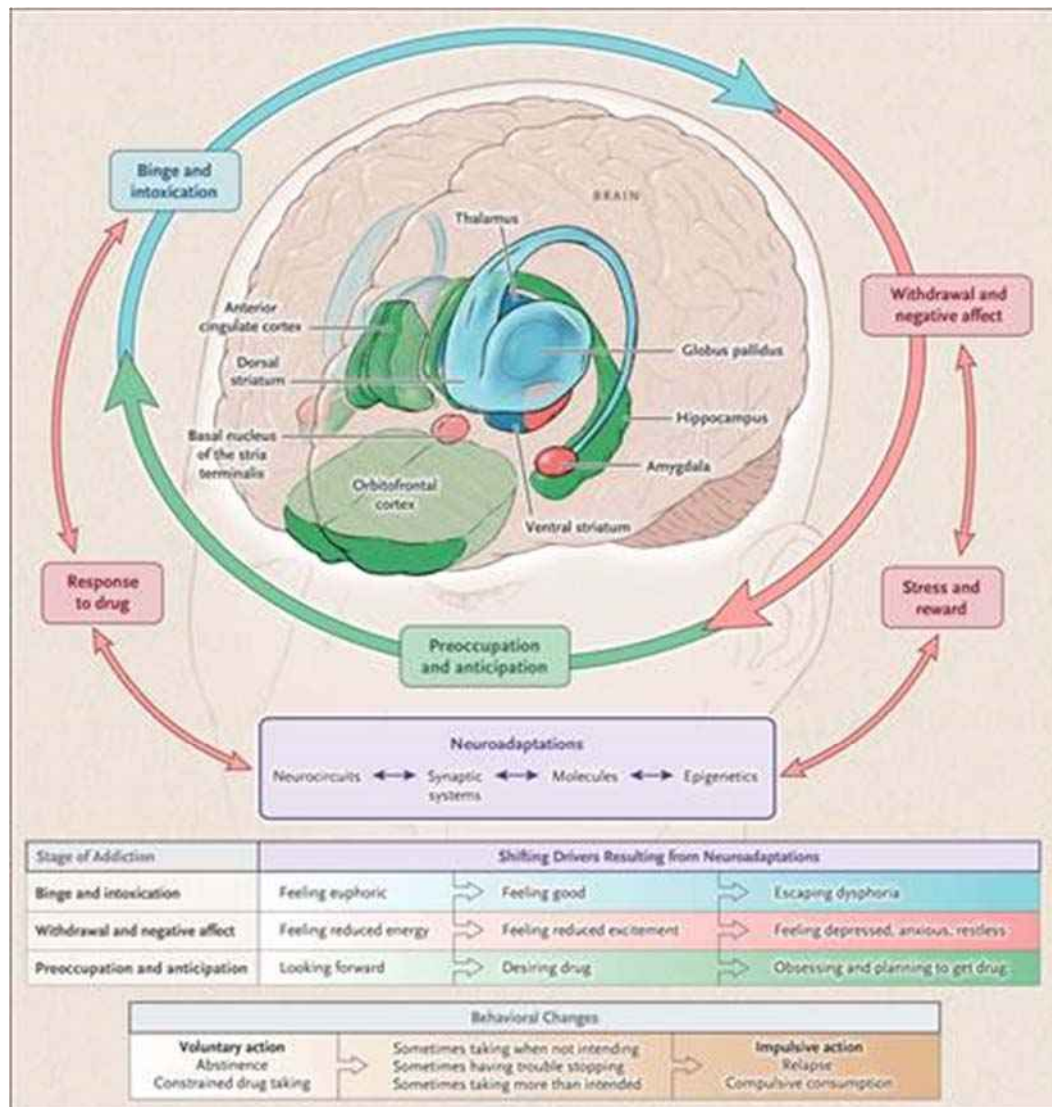
⁴⁰ Koob GF, Volkow ND. Neurocircuitry of addiction. *Neuropsychopharmacology*. 2010;35:217-238. doi:10.1038/npp.2010.4.

own endogenous dopamine receptors. This process is called neuroadaptation, and the result is a dopamine deficit state, wherein the threshold for experiencing pleasure goes up, and the threshold for experiencing pain goes down. Addicted individuals then need the substance not to feel good, but to escape the pain of withdrawal.

- ii. In severe forms of addiction, individuals commit all available resources to obtaining more of the substance, even forgoing natural rewards like food, finding a mate, or raising children.⁴¹ By hijacking the brain's reward and motivational centers, addiction leads to compulsive, self-destructive consumption that overcomes the limits of voluntary choice. The cycle of neuroadaptation is illustrated below⁴²:

⁴¹ Schultz W. Potential vulnerabilities of neuronal reward, risk, and decision mechanisms to addictive drugs. *Neuron*. 2011;69(4):603-617. doi:10.1016/j.neuron.2011.02.014.

⁴² Volkow, ND., *et al.*, Neurobiologic Advances from the Brain Disease Model of Addiction. *N Engl J Med*. 2016; 374:363-371, Figure 1.

Cycle of Neuroadaptation⁴³

g. Because addiction affects the same neural pathways evolved over millions of years to encourage humans to seek out pleasure and avoid pain, everyone is vulnerable to the disease of addiction.

i. Or as Nora Volkow, Director of the National Institute on Drug Abuse, and Thomas McLellan, former Deputy Director of the Office of National Drug Control Policy, wrote in their review “Opioid Abuse in Chronic Pain” in the *New England Journal of Medicine* (2016), “no patient is immune to addiction.”⁴⁴ Similarly,

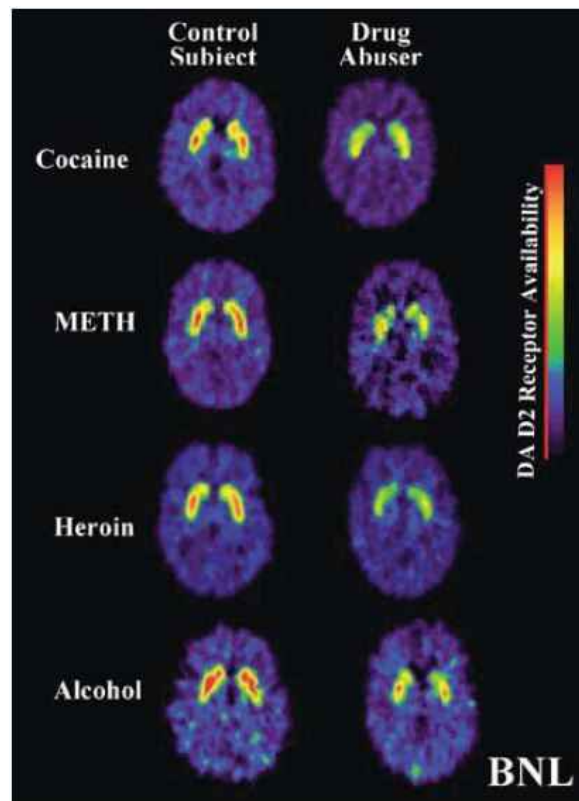
⁴³ *Id.*

⁴⁴ Volkow ND, McLellan AT. Opioid Abuse in Chronic Pain - Misconceptions and Mitigation Strategies. *N Engl J Med.* 2016;374(13):1253-1263. doi:10.1056/NEJMr1507771, at p. 1254.

as stated by the CDC, “Anyone who takes prescription opioids can become addicted to them.”⁴⁵

- ii. Without activation by consumption of the drug, the disease of addiction does not exist. This is supported by studies that have identified a dopamine receptor deficit state among those exposed to addictive drugs, compared to healthy subjects who have not been exposed, as illustrated below.⁴⁶

The Effect of Addiction on Dopamine Receptors⁴⁷



- h. Exposure to/consumption of the addictive substance is a necessary criterion for the development of addiction to that substance. One of the biggest risk factors for becoming addicted to a substance is simple exposure to that substance.

⁴⁵ Centers for Disease Control and Prevention. *Prescription Opioids*.

<https://www.cdc.gov/drugoverdose/opioids/prescribed.html> (last updated August 29, 2017)

⁴⁶ Koob *et.al*, “Neurocircuitry,” fn.40, above, p. 223; Volkow ND, Fowler JS, Wang G-J, Swanson JM. Dopamine in drug abuse and addiction: results from imaging studies and treatment implications. *Mol Psychiatry*. 2004;9(6):557-569. doi:10.1038/sj.mp.4001507 at p. 557.

⁴⁷ Volkow ND, Fowler JS, Wang GJ, Swanson JM, Telang F. Dopamine in drug abuse and addiction: results of imaging studies and treatment implications. *Arch Neurol*. (2007) 64:1575–9. 10.1001/archneur.64.11.1575 at p. 6.

- i. The current opioid epidemic is a tragic and compelling example of increased access leading to increased addiction and related death. The quadrupling of opioid prescribing between 1999 and 2012, combined with widespread distribution of those opioids to every corner of America, does not merely correlate with rising rates of opioid addiction and related deaths, it is causative.
- i. A Task Force appointed by the Association of Schools and Programs in Public Health (ASPPH), issued a Report on November 1, 2019, concluding, “The *tremendous expansion of the supply* of powerful (high-potency as well as long-acting) prescription opioids led to scaled increases in prescription opioid dependence, and the transition of many to illicit opioids, including fentanyl and its analogs, which have subsequently driven exponential increases in overdose.”⁴⁸ The report also stated that addiction, or Opioid Use Disorder, “is caused by repeated exposure to opioids.”⁴⁹ ASPPH consists of over 120 member institutions accredited by the Council on Education for Public Health, including including 7 programs in the state of Ohio.⁵⁰ The Task Force was appointed by the ASPPH board of directors, and was composed of 14 “recognized experts in the field.” I agree with these statements of the ASPPH Task Force, which are consistent with, and supportive of, the opinions I have expressed in this Report, and in my work prior to becoming involved in litigation related to the opioid epidemic.
- ii. In their 2017 report “Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use,” The National Academies of Science, Engineering and Medicine (NASEM) cited “heavy promotion of opioid prescribing by drug manufacturers (including misleading claims by some) and substantially increased prescribing” as contributors to the widespread availability and exposure to prescription opioids.⁵¹
- iii. The NASEM Report also found that diversion is a key contributor to increased exposure to prescription opioids. Prescription drugs

⁴⁸ ASPPH Report, “Bringing Science to Bear on Opioids,” fn.16, above, at p. 8 (emphasis added).

⁴⁹ *Id.*, at p. 10.

⁵⁰ *Id.* at pp. 2-3, 56. Ohio-based Member Institutions include Case Western Reserve University MPH Program, Consortium of Eastern Ohio Master of Public Health Program, Kent State University College of Public Health, Ohio State University College of Public Health, University of Cincinnati College of Medicine MPH Program, University of Toledo Master of Public Health Program and Wright State University MPH Program.

⁵¹ National Academies of Science Engineering and Medicine (NASEM). *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use*; 2017. doi:10.17226/24781, at pp. 40-41 (emphasis added).

are diverted to nonmedical use in several ways: (1) diversion before a prescription has been filled (*e.g.*, theft from production facilities or retail pharmacies), (2) diversion via the filling of a prescription (*e.g.*, pursuant to doctor shopping and high-frequency prescribers, etc.) and (3) diversion after a prescription has been filled (*e.g.*, by subsequent transfer or sale to a third party). “The DEA (2016b, p. 34) reports that in recent years, distributors in the United States disbursed 12-15 billion dosage units of opioid narcotics to retail-level purchasers, suggesting that total diversion is on the order of 2.5-4.0 billion dosage units.”⁵² A *Washington Post* analysis of federal ARCOS data shows that from 2006-2014, more than 100 billion oxycodone and hydrocodone pills were delivered in the United States.⁵³ At the same rate of diversion reported by NASEM for the period it reviewed, that would represent diversion on the order of 15.8-25 billion pills during the nine year period from 2006-2014.

- iv. Likewise, decreased supply of addictive substances decreases exposure and risk of addiction and related harms. Two natural experiments in the last century tested and proved this hypothesis. The first was Prohibition, a nationwide constitutional ban on the production, importation, transportation, and sale of alcoholic beverages from 1920 to 1933, which led to a sharp decrease in the number of Americans consuming and becoming addicted to alcohol.⁵⁴ (There were other unintended consequences of Prohibition, but the positive impact on alcohol consumption and related morbidity is widely under-recognized.) Second, many soldiers in Vietnam during the Vietnam War became addicted to opioids, most of whom stopped using opioids on their return to the United States, where access was limited.⁵⁵
- j. Opioids are different from other addictive substances for the following reasons:
 - i. They are sold as medicine, normalizing their use and propagating a misleading safety profile, with devastating consequences.

⁵² *Id.* at p. 223.

⁵³ Steven Rich, Scott Higham and Sari Horwitz *More than 100 Billion Pain Pills Saturated the Nation over Nine Years*, Washington Post, January 14, 2020.

⁵⁴ Hall W. What are the policy lessons of National Alcohol Prohibition in the United States, 1920-1933? *Addiction*. 2010. doi:10.1111/j.1360-0443.2010.02926.x, at p. 105.

⁵⁵ Robins LN, Davis DH, Nurco DN. How permanent was Vietnam drug addiction? *Am J Public Health*. 1974;64(12 Sup):38-43. doi:10.2105/AJPH.64.12_Suppl.38, at p. 40.

- ii. They kill quickly, such that even a single exposure in an opioid naïve person can lead to death.
- They create a debilitating dependence such that painful withdrawal leads to a vicious cycle of drug-seeking and withdrawal, as discussed in Section §C.10 of this Report, below.

3. Opioid prescribing began to increase in the 1980s and became prolific in the 1990s and the early part of the 21st century, representing a radical paradigm shift in the treatment of pain and creating more access to opioids across the United States.

- a. Prior to 1980, doctors used opioid pain relievers sparingly, and only for the short term in cases of severe injury or illness, during surgery, or at the very end of life.⁵⁶ Doctors' reluctance to prescribe opioids stemmed from the legitimate concern that patients would get addicted.
- b. Opioid prescribing tripled between the 1990s and 2012, and dramatically increased in dose and duration. "By 2010, enough OPR [opioid pain relievers] were sold to medicate every American adult with a typical dose of 5 mg of hydrocodone every 4 hours for 1 month."⁵⁷
 - i. From 1996 to 2011 there was a 1,448% increase in the medical use of opioids, with increases of 690% from 1995 to 2004 and 100% from 2004 to 2011. Over the same time period, opioid misuse increased more dramatically: 4,680% from 1996 to 2011, with increases of 1,372% from 1996 through 2004 and 245% from 2004 to 2011. The number of patients seeking treatment for opioid use disorder in this time period, not including heroin, increased 187%, whereas treatment-seeking increased 87% for heroin, 40% for cannabis, and decreased 7% for cocaine use disorder.⁵⁸ The increase in the medical use of opioid analgesics during this time period substantially contributed to increases in misuse and addictive use. The chart below,⁵⁹ based on official government data,⁶⁰ shows this close relationship:

⁵⁶ Meldrum ML. *Opioids and Pain Relief: A Historical Perspective (Progress in Pain Research and Management, V. 25)*. IASP Press; 2003, at pp. 195-199.

⁵⁷ Paulozzi LJ, Jones CM, Mack K a, Rudd R a. Vital Signs: Overdoses of Prescription Opioid Pain Relievers --- {United States}, 1999–2008. *MMWR Morb Mortal Wkly Rep.* 2011;60(43):1487-1492, http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm?s_cid=mm6043a4_w, at p. 1489.

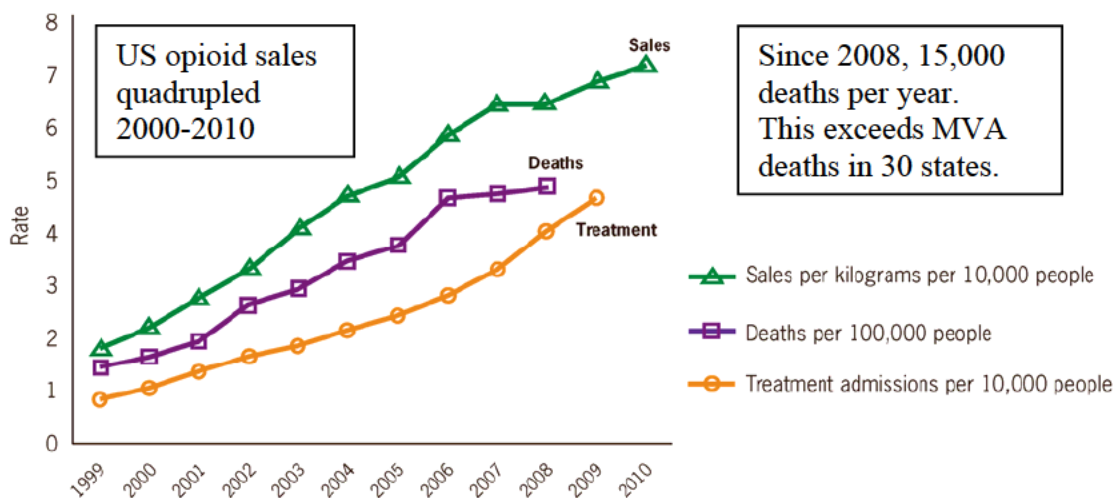
⁵⁸ Atluri S, Sudarshan G, Manchikanti L. Assessment of the trends in medical use and misuse of opioid analgesics from 2004 to 2011. *Pain Physician.* 2014, at p. E119.

⁵⁹ Reproduced from Sullivan MD, *et al.*, Opioid therapy for chronic pain in the US. *Pain* 2013; 154:S94-100, Fig.2.

⁶⁰ Centers for Disease Control and Prevention. *Prescription Painkiller Overdoses in the US infographic.* <https://www.cdc.gov/vitalsigns/painkilleroverdoses/infographic.html>, (last updated November 1, 2011).

CDC: Parallel increases in opioid sales, deaths and substance abuse

Rates of prescription painkiller sales, deaths and substance abuse treatment admissions (1999-2010)



SOURCES: National Vital Statistics System, 1999-2008; Automation of Reports and Consolidated Orders System (ARCOS) of the Drug Enforcement Administration (DEA), 1999-2010; Treatment Episode Data Set, 1999-2009

- ii. A study by Paulozzi *et al*, published in 2006, analyzed death certificates from 1999-2002, and found that the most rapidly increasing category of death certificate-reported mortality was “opioid analgesic without heroin or cocaine,” which rose 129.2% in that time period, compared to deaths associated with heroin alone (without prescription opioids or cocaine), which rose only 23.7%, and cocaine alone, which rose 16%.⁶¹ Paulozzi stated, “Overall, the relative increase in ARCOS opioid sales (76%) from 1999 to 2002 was consistent with the relative increase in opioid poisoning (95%).”⁶²
- iii. The Paulozzi article also reported a 73% increase in opioid-analgesia-related emergency department visits between 1999-2002.⁶³ Paulozzi *et al*’s conclusion was that prescription opioids alone were the principal cause of death during the early years of the opioid epidemic,⁶⁴ with illicit drugs becoming more prevalent in later years, in part due to the higher cost and/or lesser availability of prescription opioids.

⁶¹ Paulozzi LJ, *et. al*. Increasing deaths from opioid analgesics in the United States. *Pharmacoepidemiology and Drug Safety*. 2006;15:618-627, at p. 621.

⁶² *Id.*, at p. 624

⁶³ *Id.*

⁶⁴ *Id.*, at p. 626.

- iv. Consistent with Paulozzi's findings, Ohio data show prescription opioid-related deaths were the first and primary driver of opioid-related deaths in the state. In 2008, prescription opioids were involved in more unintentional overdoses (40%) than heroin and cocaine combined (33%) in Ohio.⁶⁵ In 2012, the number of heroin-related deaths in Ohio began to surpass those of prescription opioids,⁶⁶ as "heroin has become a cheaper alternative for prescription opioid users."⁶⁷ By 2019, 76.2% of overdose deaths in Ohio involved illicit fentanyl or fentanyl analogs.⁶⁸ Ohio data also show "a strong relationship between increases in sales of prescription opioids and fatal unintentional drug poisoning rates" in the state of Ohio.⁶⁹ From 1999 to 2007, total grams of prescription opioids distributed in the state rose 325% while Ohio's death rate due to unintentional drug poisonings "driven largely by prescription drug overdoses" increased 304%.⁷⁰ In 2013, an Ohio House of Representatives report stated unequivocally that "There is a direct correlation between the number of overdose cases and the rise in opioid prescriptions."⁷¹ The relationships between Ohio prescription opioid supply, overdose and related harms are graphically illustrated in the charts below:⁷²

⁶⁵ Ohio Department of Health, Violence and Injury Prevention Program, "Epidemic of Prescription Drug Overdose in Ohio", https://odh.ohio.gov/wps/wcm/connect/gov/5a0bbf8a-8d88-49e5-bd6c-56ca28c2104c/Epidemic_of_Prescription_Drug_Overdose_Ohio_Report.pdf?MOD=AJPERES&CONVERT_TO=url&CACHEID=ROOTWORKSPACE.Z18_M1HGGIK0N0JO00QO9DDDDM3000-5a0bbf8a-8d88-49e5-bd6c-56ca28c2104c-miUpbk3, at p. 2.

⁶⁶ Massatti R, Beeghly C, Hall O, Kariisa M, Potts L. Increasing heroin overdoses in Ohio: understanding the issue. Columbus, OH: Ohio Department of Mental Health and Addiction Services; 2014, at p. 3 and Figure 2.

⁶⁷ *Id.*, at p. 4.

⁶⁸ Ohio Department of Health, "2019 Ohio Drug Overdose Data: general findings" (November 6, 2020). https://odh.ohio.gov/wps/wcm/connect/gov/0a7bdcd9-b8d5-4193-a1af-e711be4ef541/2019_OhioDrugOverdoseReport_Final_11.06.20.pdf?MOD=AJPERES&CONVERT_TO=url&CACHEID=ROOTWORKSPACE.Z18_M1HGGIK0N0JO00QO9DDDDM3000-0a7bdcd9-b8d5-4193-a1af-e711be4ef541-nmv3qSt, at p. 1.

⁶⁹ Ohio Department of Health, "Epidemic", fn. 65, above, at p. 2.

⁷⁰ *Id.*, at pp. 1-2.

⁷¹ Ohio House of Representatives, *Prescription Drug Addiction and Healthcare Reform Legislative Study Committee Chairman's Report*. (October 17, 2013), <https://ohiohouse.gov/assets/press-releases/28803/files/6923.pdf>, at p. 5. See also, ABDCMDL00139503.

⁷² Ohio Department of Health. "Ohio's Prescription Drug Overdose Epidemic: Epidemiology, contributing factors and ongoing prevention efforts" (April 17, 2014). <http://web.archive.org/web/20161201222703/http://www.healthy.ohio.gov/-/media/HealthyOhio/ASSETS/Files/injury-prevention/2012-overdose-data/1Drug-poisoning-Oct-2014.pdf?la=en>, at p 39; Ohio Department of Health, "Epidemic", fn. 65, above, at p. 5 (Figure 10).

There is a strong relationship between increases in exposure to prescription opioids and fatal unintentional overdose rates.

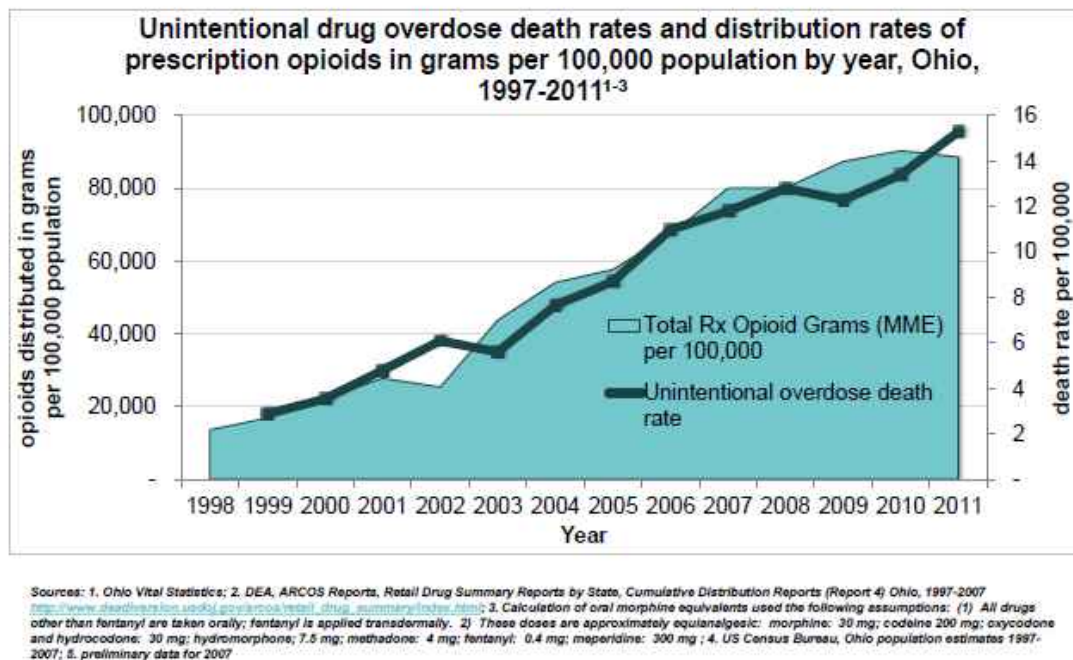
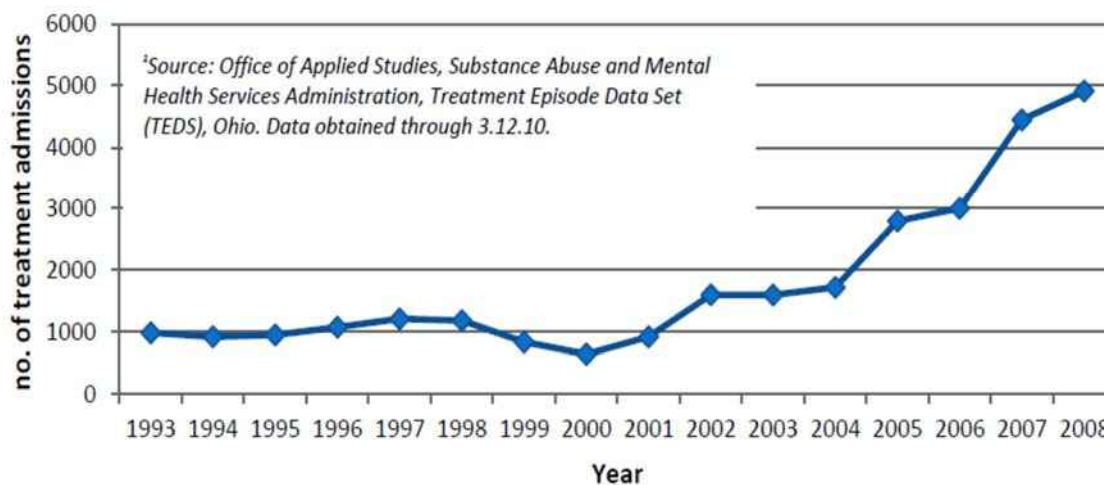


Figure 10. Number of substance abuse treatment admissions for non-heroin opioids by year, Ohio, 1993-2008¹



- v. “By 2005, long-term opioid therapy was being prescribed to an estimated 10 million US adults. The volume of prescribed opioid analgesics was 100 MME [Morphine Milligram Equivalent] per person in 1997; in 2007, the

MME per person had increased to almost 700 MME.”⁷³ By 2017, the level of MME had declined from its peak to 543.4 MME, which remains well over 5 times higher than the prescribing rate in 1997.⁷⁴

- vi. The number of long-term opioid users (daily for greater than 90 days) increased between 1999 and 2014. “Of all opioid users in 2013-2014, 79.4% were long-term users compared with 45.1% in 1999-2000.”⁷⁵ The increase in long-term use is important, because increased duration of use is also directly correlated with risk of addiction.⁷⁶
- vii. Between 2006 and 2015, 66% of patients receiving an opioid prescription in an ambulatory (outpatient) care setting had a diagnosis of non-cancer pain, and 28% had no pain diagnosis at all. Only 5% of patients had a cancer-related pain diagnosis. Absence of a pain diagnosis was more common in visits where an opioid prescription was continued (30.5%) than those in which an opioid was newly prescribed (22.7%).⁷⁷
- viii. As reported in an article I co-authored in 2016, more than one-third of Part D Medicare enrollees fill at least one opioid prescription in any given year. Part D covers 68% of the roughly 55 million people on Medicare.⁷⁸ As such, more than 10 million Part D Medicare enrollees are exposed to a prescription opioid in any given year, thus becoming vulnerable to the adverse effects of opioids, including but not limited to addiction. Medicare represents just one patient population, suggesting that many millions of patient consumers in this country have been exposed to the risks of prescription opioids in recent decades, both within and outside the Medicare-eligible populations.⁷⁹
- ix. In an evaluation of over one million Medicaid enrollees, one out of five pregnant women (21.6%) filled an opioid prescription. From 1992 to

⁷³ Paulozzi LJ, Weisler RH, Patkar A a. A national epidemic of unintentional prescription opioid overdose deaths: how physicians can help control it. *J Clin Psychiatry*. 2011;72(5):589-592. doi:10.4088/JCP.10com06560, at p. 589.

⁷⁴ Schieber LZ, Guy, GP, Seth P, *et al*. Trends and Patterns of Geographic Variation in Opioid Prescribing Practices by State, United States, 2006-2017. *JAMA Netw Open*. 2019;2(3):e190665, at p. 1.

⁷⁵ Mojtabai R. National trends in long-term use of prescription opioids. *Pharmacoepidemiol Drug Saf*. 2017. doi:10.1002/pds.4278, at p. 526.

⁷⁶ Edlund MJ, Martin BC, Russo JE, Devries A, Braden JB, Sullivan MD. The Role of Opioid Prescription in Incident Opioid Abuse and Dependence Among Individuals With Chronic Noncancer Pain. *Clin J Pain*. 2014;30(7):557-564, at p. 557.

⁷⁷ Sherry TB, Sabety A, Maestas N. Documented Pain Diagnoses in Adults Prescribed Opioids: Results From the National Ambulatory Medical Care Survey, 2006–2015. *Ann Intern Med*. 2018;169(12):892-894, at p. 892.

⁷⁸ Lembke *et al.*, “Use of Opioid Agonist Therapy”, fn.7, above, at pp. 990-991.

⁷⁹ A recent study by Romman is consistent with our own findings, *see, e.g.*, Romman AN, *et al*. Opioid Prescribing to Medicare Part D Enrollees, 2013-2017: shifting responsibility to pain management providers. *Pain Medicine*. 2020; 0(0): 1-9.

2012, the proportion of pregnant women admitted to substance abuse treatment facilities that reported a history of prescription opioid addiction increased from 2% to 28%.⁸⁰

- c. As reported in another article I co-authored in 2016, increased opioid prescribing is distributed across different types of prescribers, relatively indifferent to individual physicians, specialty, or region.⁸¹
 - i. In other words, opioid overprescribing is not merely the result of a small subset of so-called “pill mill” doctors, although such doctors do exist and have contributed to the current epidemic. Doctors across diverse medical specialties are prescribing more opioids.
 - ii. By specialty, pain doctors prescribe more opioids than doctors in any other specialties. However, by volume, family medicine and internal medicine doctors account for the most opioids, because there are more of them.⁸²
 - iii. But the salient finding was that the increase in opioid prescribing is not explained by a minority of prolific prescribers alone. Rather, opioid prescribing has increased broadly across a variety of specialties.⁸³
- d. A recent peer-reviewed publication evaluated prescriptions and diagnoses among enrollees in both commercial and Medicaid databases, and found that of 99,395 commercially insured and 60,492 Medicaid patients with an OUD diagnosis between 2005-2015, “most enrollees with OUD in the data had current opioid prescriptions.”⁸⁴ This supports the conclusion that prescription opioids are intertwined with opioid addiction, and that the paradigm shift in medicine toward liberal opioid prescribing has been a major factor contributing to the increased supply which has fueled this opioid epidemic.
- e. Although national average opioid prescribing has plateaued or decreased since its peak in 2012, overall opioid prescribing in the US remains at levels far exceeding pre-1990 rates, and greater than in other countries with comparable needs for analgesia.

⁸⁰ Krans EE, Patrick SW. Opioid Use Disorder in Pregnancy: Health Policy and Practice in the Midst of an Epidemic. *Obstet Gynecol.* 2016 July; 128(1): 4-10, at p. 4. Opioid exposure during pregnancy increases the occurrence of Neonatal Abstinence Syndrome (NAS), a condition resulting in acute effects among newborns and long-term developmental delays. See discussion of NAS in Section §C.10.bb. of this Report.

⁸¹ Chen et.al, “Distribution of Opioids”, fn.5, above, at p. 260.

⁸² *Id.* at pp. 259-260.

⁸³ *Id.* at p. 260.

⁸⁴ Ali MM, *et al.*, Opioid Use Disorder and Prescribed Opioid Regimens: Evidence from Commercial and Medicaid Claims, 2005-2015. *J Med Toxicol.* 2019 Jul;15(3):156-168. doi: 10.1007/s13181-019-00715-0. Epub 2019 May 31, at p. 156. The authors state, “This suggests that opioids prescribed for pain continue to lead to the development of dependence and misuse.” *Id.*, at 164. This statement supports my opinions concerning the “Gateway Effect,” as discussed in Section §C.9 of this Report.

- i. The U.S. national average number of opioid prescriptions written in 2012 was 81 opioid prescriptions per 100 persons (255 million total prescriptions). By 2016, the U.S. national average had decreased to 66 opioid prescriptions per 100 persons (214 million total). In 2017, the prescribing rate had fallen to its lowest in more than 10 years, at 59 prescriptions per 100 persons (total of more than 191 million total opioid prescriptions).⁸⁵
 - ii. However, prescribing rates in the United States are still greater than in the late 1990s, and greater than in other countries with comparable needs for analgesia. Further, in certain regions of the United States, opioid prescribing continues to remain very high, well above the national average. In 2017, according to the CDC, “In 16% of U.S. counties, enough opioid prescriptions were dispensed for every person to have one.” And “some counties had rates that were seven times higher than that.”⁸⁶
 - iii. Among 48 million individuals with any period of insurance coverage between January 2007 and December 2016, including commercial beneficiaries, Medicare Advantage beneficiaries aged 65 years and over, and Medicare Advantage beneficiaries under age 65 years (eligible owing to permanent disability), data show that prescription opioid use and average daily dose measured at the individual level have not substantially fallen from their peaks. “Across all years of the study, annual opioid use prevalence was 14% for commercial beneficiaries, 26% for aged Medicare beneficiaries, and 52% for disabled Medicare beneficiaries.”⁸⁷
- f. Opioid prescribing in the United States far exceeds that of other developed nations with aging populations and comparable population needs for pain relief.
- i. Using International Narcotics Control Board figures, the United States consumed 173,332 kilograms of 574,693 kilograms of opioids consumed globally (382,131.6 of 1,266,981.2 pounds), or 30.2 percent.⁸⁸
 - ii. Using “defined daily doses,” the United States consumed the most opioids per unit population from 2013 to 2015: 47,580 doses of narcotic drugs were consumed per day per million people. Canada comes in second with

⁸⁵ Centers for Disease Control and Prevention. *U.S. Opioid Prescribing Rate Maps*. <https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html>.

⁸⁶ *Id.*

⁸⁷ Jeffery MM, Hooten WM, Henk HJ, *et al.* Trends in opioid use in commercially insured and Medicare Advantage populations in 2007-16: retrospective cohort study. *BMJ*. 2018;362:k2833. doi:10.1136/bmj.k2833, at p. 1.

⁸⁸ International Narcotics Control Board, *Narcotic Drugs Technical Report 2016*, at pp. 200-203. *See* https://www.incb.org/incb/en/narcotic-drugs/Technical_Reports/2016/narcotic-drugs-technical-report-2016.html.

34,444 defined doses consumed per million people per day, and Germany in third with 30,796; Japan was 50th at 1,223 defined doses/day.⁸⁹

■ In summary, opioid prescribing was appropriately limited prior to the expanded uses that began in the 1980s and proliferated in the 1990s and beyond. As detailed in the following sections of this Report, such increased use of opioids was driven by misleading messages that downplayed risks and overstated benefits, and by widespread promotion, distribution, and dispensing that enabled overexposure to occur.

4. The Pharmaceutical Opioid Industry contributed substantially to the paradigm shift in opioid prescribing through misleading messaging about the safety and efficacy of prescription opioids. The Industry disseminated these misleading messages through an aggressive sales force, key opinion leaders, medical school curricula, continuing medical education courses, clinical decision support tools, professional medical societies, patient advocacy groups, the Federation of State Medical Boards, and The Joint Commission.

- a. The Pharmaceutical Opioid Industry targeted doctors and patients by creating an aggressive sales force, by promoting key opinion leaders, by infiltrating medical school and continuing medical education courses, by supporting professional medical societies, by influencing electronic medical record systems, and by co-opting medical watchdog organizations like the Federation of State Medical Boards and The Joint Commission to convince prescribers and the broader health care system that liberal opioid prescribing is based on science, and that failing to prescribe opioids is tantamount to causing pain. They misrepresented marketing as education and used flawed and biased studies to achieve this goal. These misrepresentations were transmitted to medical students, residents, and physicians, leading to a paradigm shift in opioid prescribing, such that opioids became first-line treatment for minor and chronic pain conditions. In fact, there has never been sufficient evidence to justify widespread opioid prescribing. These actions directly contributed to the opioid epidemic we face today.⁹⁰
- b. As stated by the National Academies of Sciences, Engineering and Medicine, “on the supply side, weak government regulations and aggressive and highly effective marketing tactics on the part of the pharmaceutical industry (manufacturers, distributors, pharmacies) and pain management advocacy groups (many of which

⁸⁹ *Id.* at pp. 226-228.

⁹⁰ As stated in a 2019 study, “The contribution of prescription opioids to the sharp rise in overdose deaths in the United States began in the late 1990’s and is primarily an iatrogenic problem, driven by an increase in opioid prescribing for persistent pain. The drivers of this increase are complex, including factors within the health care system (eg, adoption of the pain scale as the fifth vital sign, aligning physician incentive payments with patient satisfaction, pharmaceutical industry marketing) and public expectations for pain treatment.” Hedberg K, et al. Integrating public health and health care strategies to address the opioid epidemic: the Oregon Health Authority’s opioid initiative. *Journal of Public Health Management & Practice*. 2019;25(2):214-220, at p. 219. As detailed in this section of the Report, the Pharmaceutical Opioid Industry promoted the “drivers” referenced in the quoted text, including the “fifth vital sign” and “patient satisfaction” based on pain scores.

were funded by the pharmaceutical industry) and physicians sparked a massive increase in opioid prescribing in the 1990s and 2000s and the subsequent rise in prescription opioid misuse, addiction and overdose (Kolodny et al. 2015).”⁹¹

c. Aggressive Sales Force

- i. As explained below, the Pharmaceutical Opioid Industry retained an aggressive sales force incentivized to target doctor’s offices and pharmacies to increase sales, thereby increasing the number of people exposed to opioids.
- ii. In 2012 the pharmaceutical industry spent \$15 billion on face-to-face sales and promotional activity.⁹² These face to face promotional activities rely primarily on sales representatives (drug reps) who market their products directly to doctors’ offices and pharmacies.⁹³ The Pharmaceutical Opioid Industry uses a host of proven strategies to influence doctor prescribing, including but not limited to: a lucrative bonus system, sophisticated databases to target doctors who are already prolific prescribers with a large population of pain patients, intensive sales training to provide specific language for how to talk to prescribers, speakers’ bureaus to disseminate promotional messaging to large groups of doctors all at once, free samples/coupons/vouchers for opioid drugs, branded promotional items such as “Oxycontin fishing hats, stuffed plush toys, and music compact discs,” free meals,⁹⁴ and, in my experience, steaming cups of hot coffee delivered right to the office door.
- iii. A 2018 study by Hadland et al found that marketing of opioid products across U.S. counties was associated with increased prescribing.⁹⁵ Although the authors cautiously described their findings as ‘associations’ rather than ‘causal associations,’ in a Reply to a Letter to the Editor of *JAMA Internal Medicine* concerning the 2018 publication, Hadland cited several traditional factors considered by epidemiologists to infer causality: (1) “temporality between exposure and outcome,” to ensure that “prescribing changes occurred after marketing was received;” (2) findings

⁹¹ National Academies of Sciences, Engineering and Medicine (NASEM) 2021. *High and Rising Mortality Rates Among Working-Age Adults*. Washington, DC. The National Press. <https://doi.org/10.17226/25976>, at p. 7-19 [prepublication copy]

⁹² Pew Charitable Trust, “Persuading the Prescribers: Pharmaceutical Industry Marketing and its Influence on Physicians and Patients. (November 11, 2013). <https://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2013/11/11/persuading-the-prescribers-pharmaceutical-industry-marketing-and-its-influence-on-physicians-and-patients>

⁹³ *Id.*

⁹⁴ Van Zee A. The promotion and marketing of oxycontin: Commercial triumph, public health tragedy. *Am J Public Health*. 2009. doi:10.2105/AJPH.2007.131714, at pp. 221-222. *See also*, Pew, “Persuading the Prescribers”, fn. 92, above.

⁹⁵ Hadland SE, et al. Association of Pharmaceutical Marketing of Opioid Products to Physicians with Subsequent Opioid Prescribing. *JAMA Internal Medicine*. 2018;178(6):861-863.

that were “consistent with other research showing that physicians who receive pharmaceutical industry payments prescribe more of the medications being marketed;” and (3) “dose-response,” with “each additional industry-sponsored meal associated with greater subsequent prescribing.”⁹⁶

- iv. Temporality, consistency, and dose-response are all among the factors cited in a seminal 1965 article by Sir Austin Bradford Hill, establishing a well-recognized methodology to determine causality between an intervention or exposure and an outcome.⁹⁷ Hadland also stated, “It is unlikely that pharmaceutical companies would invest so heavily in direct-to-physician marketing if it did not increase or at least maintain current levels of prescribing.”⁹⁸ See Section §C.13 below, for the role of the Bradford-Hill factors in this case.
- A 2019 study by Hadland *et al.*, found that “across US counties, marketing of opioid products to physicians was associated with increased opioid prescribing and, subsequently, with elevated mortality from overdoses.” The authors go on to say that “Amid a national opioid overdose crisis, reexamining the influence of the pharmaceutical industry may be warranted.”⁹⁹ It is my opinion in light of the totality of evidence, including the parallel increases in sales, marketing, and opioid mortality over a 20+ year period, (see Sections §C.3.b., above, and Section §C.12.b, below) as well as the specific relationships documented by Hadland,¹⁰⁰ that there is a cause and effect relationship between promotion of opioids through false and misleading statements of low risk and substantial benefit, increased opioid prescribing, and opioid-related mortality.
- vi. A 2007 performance evaluation of an Endo sales representative demonstrates these effects: “one on one dinners and lunches have greatly attributed [sic] to your Opana [sales] growth... You utilizes [sic] the selling technology afforded to you by the Endo Selling model and engendering thoughts with your clients. I most recently observed this with Dr. Helms where you got him to see that he was too conservative in dosing Opana in the past and to agree to try Opana again on a patient he was seeing that very week.”¹⁰¹

⁹⁶ Hadland SE, *et al.* In Reply. *JAMA*. 2018;178(10):1426-1427.

⁹⁷ Hill AB, The Environment and Disease Proceedings of the Royal Society of Medicine. 1965;58(5) :295-300.

⁹⁸ Hadland SE, *et al.* In Reply. *JAMA*. 2018;178(10):1426-1427., above at p. 1426.

⁹⁹ Hadland SE, *et al.* Association of Pharmaceutical Industry Marketing of Opioid Products with Mortality from Opioid-Related Overdoses. *JAMA Network Open*. 2019;2(1):e186007, at p. 1.

¹⁰⁰ *Id.*, see also Hadland SE, *et al.* Industry Payments to Physicians for Opioid Products, 2013-2015. *Am J Public Health*. 2017;107:1493-1495; Hadland SE, *et al.* Association of Pharmaceutical Marketing of Opioid Products to Physicians with Subsequent Opioid Prescribing. *JAMA Internal Medicine*. 2018;178(6):861-863.

¹⁰¹ ENDO-CA-00110114 at -0119

- vii. An Endo “2009 OPANA Brand Strategic Plan,” shows the importance of Endo’s sales representatives to their promotion of opioid products.¹⁰² Endo targeted the highest volume prescribers, while also working to recruit new prescribers.¹⁰³
- viii. The Endo “2009 OPANA Brand Strategic Plan” focused on “the highest OPANA ER potential customers by adjusting targeting for greater sales call efficiency.” “Focus on PCPs [Primary Care Physicians] who act like pain specialists.” This “focus” was significant, because Endo’s Plan recognized that “Pain Specialists Are Most Productive.”¹⁰⁴ While pain specialists account for only 15% of the prescribers, they accounted for 30% of the prescriptions.¹⁰⁵ Endo advocated “targeting for more efficient deployment of resources on highest potential targets.”¹⁰⁶ This is relevant to the issue of reverse causation. Reverse causation in this context posits that the promotional efforts of the pharmaceutical industry were directed to the most prolific opioid prescribers because they were already prescribing more opioids. But this document makes it clear that Endo specifically targeted high prescribers because their promotional efforts to this group yielded even more opioid prescribing. Projected sales support in 2009 for Endo drug reps was more than \$3 million, indicating the value of the sales representatives to Endo’s Strategic Plan to increase sales.¹⁰⁷
- ix. Not only were opioid drug reps encouraged to disseminate the same misleading messages about opioid risks and benefits as detailed in this report; they were also a source of free drugs via samples,¹⁰⁸ coupons, and vouchers, which in turn promoted easy access to opioids, a known risk for opioid addiction and overdose death. Endo promoted its Instant Savings Card (ISC) for Opana and Opana ER: “Save up to \$25.”¹⁰⁹ This campaign boosted Endo’s sales: “The ROI for the OPANA ER ISC Programs ranges from 1600-9700%.”¹¹⁰ By their own analysis, 20% of ISC cards were used for three or more months, “indicating increasing brand loyalty”¹¹¹ and also leading to ongoing exposure to opioids. As will be shown in subsequent sections of this report, the longer patients are on opioids, the more likely they are to become addicted to them. Endo also launched a “Patient Starter Kit” which included an OPANA ER Instant Savings Card.¹¹²

¹⁰² ENDO-CHI_LIT-00023217 (produced natively).

¹⁰³ *Id.*, at *15 and *21.

¹⁰⁴ *Id.*, at *15 and *11.

¹⁰⁵ *Id.*, at *11.

¹⁰⁶ *Id.*, at *31.

¹⁰⁷ ENDO-CHI_LIT-00023217, at *81. (produced natively)

¹⁰⁸ Pew Trust, “Persuading the Prescribers”, fn. 92, above.

¹⁰⁹ *Id.*, at *66-67.

¹¹⁰ *Id.*, at *67.


¹¹¹ *Id.*



¹¹² *Id.*, at *66.

Patient Starter Kit

Maximize pull-through efforts on current/future managed care contracts in key states with a focus on Medicare Part D

- Objectives:
 - Provide patients with OPANA/OPANA ER information on the following:
 - Patient Information Brochure
 - Patient Education Booklet
 - Pain Diary
 - Instant Savings Card
- Description
 - An instant card savings to help you save up to \$300 off your next 12 OPANA/ OPANA ER prescriptions
- Timing
 - Q1-Q4
- Cost
 - \$850,000



- x. Endo business plans and reviews reported positive returns on its promotion of Opana ER and Percocet. A 2002 business review reported that the Percocet “sales message is having a positive impact on physicians,” and that “approximately 90%” indicate that they have prescribed the new strengths recently.¹¹³ Additionally, a third party analysis prepared for Endo in 2012 found that Endo’s Opana ER marketing tactics drove 19% of total sales or \$72 million dollars, with sales force detailing accounting for \$45 million of that.¹¹⁴
- xi. Actavis also marketed its products through an aggressive sales force. Deposition testimony and exhibits, summarized below, demonstrate that Actavis-trained sales personnel in positions of authority were unacceptably ill-informed about the addictive drugs they were promoting, yet nevertheless exacerbated the opioid epidemic by aggressive promotion of prescription opioids.
- xii. Actavis coordinated with inVentiv, a contract sales organization (CSO), to employ a sales force for Kadian, an Actavis morphine sulfate product. Mark Killion was employed by inVentiv, as a Regional Business Director for Kadian, from May 2009 to December 2012.¹¹⁵ In that capacity, Killion received sales training from Actavis,¹¹⁶ and Killion, in turn, supervised

¹¹³ ENDO-OPIOID_MDL-04927196 at *20 (produced natively).

¹¹⁴ ENDO-CHI_LIT-00214471 at *37 (produced natively).

¹¹⁵ Deposition of Mark Killion, In Re: Texas Opioid Litig., No. 18-0358 (Supreme Court of Texas), September 11, 2020, at 10:2-22; (hereinafter, “Texas Killion deposition”).

¹¹⁶ *Id.*, at 18:19-19:2; 21:16-24; 22:10-23:1

between 9 and 12 area sales managers promoting Kadian in Texas and the Midwest region, as well as in the West region, including California.¹¹⁷

- xiii. Mr. Killion testified that he couldn't define what an opioid was,¹¹⁸ couldn't explain tolerance,¹¹⁹ or distinguish dependence from addiction.¹²⁰ While he recognized that Kadian is addictive¹²¹ and was aware that we're in an opioid crisis driven by, in his words, "addiction of patients or people to opioid medications,"¹²² he nevertheless testified to a sales force incentivized by quotas and bonuses to increase Kadian market share,¹²³ targeting high volume prescribers for non-cancer pain.¹²⁴
- xiv. Killion testified that base salaries were paid on the basis of "sales performance," to provide an "incentive for sales results," and to "Maximize the sale of Kadian capsules."¹²⁵ Killion further testified that bonuses were paid on a percentage of a pre-specified sales quota, and that prescriptions were "dollarized," such that higher dosage Kadian had higher dollar value than lower dosage Kadian,¹²⁶ thereby incentivizing sales representatives to promote the more dangerous, higher dose product in order to earn greater bonuses.
- xv. These "dollarized" prescriptions were particularly problematic when joined with the sales representatives' training that "Kadian does not have a ceiling or recommended maximal dose" and that Kadian could be titrated upward every other day.¹²⁷ Actavis sales representatives were thus trained to promote higher and more dangerous doses of Kadian to doctors, while at the same time earning more bonus money by selling those higher and more dangerous doses.
- xvi. While Killion claims that he and Actavis sales representatives were instructed that promotion should include "fair balance" between risks and benefits,¹²⁸ that claim is refuted by the actual content of Actavis' messaging, which consistently downplayed risks of addiction while

¹¹⁷ *Id.*, at 10:9-11:11; Deposition of Mark Killion, *People of the State of California v. Purdue Pharma, L.P., et al.*, No. 30-2014-00725287-CU-BT-CXC, February 12, 2020, at 204:9-18 (hereinafter, "California Killion deposition").

¹¹⁸ Texas Killion deposition, at 18:8-10. In response to a question as to whether he could define the term addiction "in detail," Killion answered, "I can't define the term, no." In light of Killion's answer, the phrase, "in detail," in the preceding question, is irrelevant.

¹¹⁹ *Id.* at 60:21-61:17

¹²⁰ *Id.* at 63:25-64:11.

¹²¹ *Id.* at 64:13-16

¹²² *Id.* at 70:13-71:10

¹²³ California Killion deposition, at 79:5-85:22; Texas Killion deposition, at 24:11-28:15.

¹²⁴ Texas Killion deposition, at 34:24-35:15; 41:24-42:6

¹²⁵ California Killion deposition, at 79:5-83:21.

¹²⁶ *Id.*, at 83:22-86:9.

¹²⁷ Allergan MDL 00026826 at -6832.

¹²⁸ California Killion Deposition, at 211:21-212:22.

overstating claimed benefits for chronic pain, as described in Appendix I of this Report.

- xvii. The Kadian sales force promoted a \$50 coupon for co-pay assistance to thousands of doctors and pharmacies.¹²⁹ The coupon was good for repeat use up to \$600 and available direct to consumers from an online website without a prescription.¹³⁰
- xviii. The Kadian coupon program was expanded by Actavis to cover up to \$1,200 per year.¹³¹ The explicit goals of the program to “Facilitate new therapy starts”¹³² and “Increase the average length of therapy”¹³³ had the necessary consequence of increasing the population at risk of dependence, addiction, OUD, and overdose mortality.
- xix. In January 2009, immediately after it acquired the Kadian brand, Actavis implemented a co-pay program to make the drug more affordable.¹³⁴ Kadian discount cards paid up to \$50 toward a patient’s co-pay and could be used twice a month. Because the typical co-pay was \$42, most discount card users paid nothing out of pocket.¹³⁵ Between January 2009 and May 2010, Actavis circulated approximately 150,000 discount cards. Approximately 6-7% of the cards were used at least once,¹³⁶ representing between 9,000 and 10,500 individuals who were exposed to Kadian, an addictive drug at little or no cost.
- xx. The Actavis Co-Pay Program was significantly featured among the “Tactics” to promote Kadian in its sales representative training materials. For example, the sales representative materials of October 2011 cited the Co-Pay Program at multiple pages, and also described a one-page sheet called a “Shelf Talker” regarding the Co-Pay Program.¹³⁷ According to Killion’s testimony, the Shelf Talker was to be left with the Co-Pay Cards in doctors’ offices.¹³⁸ The Co-Pay Cards and the Shelf Talker combined to state that patients could save up to \$1200 per year, by re-using the same

¹²⁹ Texas Killion deposition, at 47:16-49:9 and 52:25-53:10 (testifying that Kadian co-pay assistance cards targeted to 9,000 physicians and 43,000 pharmacies); *see also* ACTAVIS0643304 (March 16, 2009 “Dear Pharmacist” email blast).

¹³⁰ *Id.* at 49:10-50:11; *see also*, Kadian website Co-Pay Assistance card request, http://web.archive.org/web/20101205163516/http://kadian.com/en/co-pay_program.htm?WBCMODE=PresentationUnpublished (last accessed October 22, 2020).

¹³¹ ACTAVIS0237771; *see also* ACTAVIS0190235(Kadian “Save up to \$1,200” brochure)

¹³² *Id.* at -7775

¹³³ *Id.*

¹³⁴ ACTAVIS0636185

¹³⁵ *Id.*

¹³⁶ *Id.*

¹³⁷ California Killion Deposition Ex. 10, ALLERGAN_MDL_00026826 at 26863-26868; California Killion deposition at 138:9-19

¹³⁸ California Killion deposition at 138:9-19; California Killion Deposition Ex. 10, Allergan_MDL_0026826 at 26865 and 26868.

card to pay the first \$50 toward each prescription for up to 24 prescriptions over 12 months; and that 87% of managed care patients could pay zero dollars with the use of the Co-Pay Cards.¹³⁹ Thus, the Kadian Co-Pay Cards provided addictive drugs essentially “free” to patients for the first year, placing them at risk of opioid-related harms by the inducement of addictive drugs at low cost, or at no cost. This type of promotion is within the scope of behavior that the 2019 ASPPH report criticized.¹⁴⁰

- xxi. Kadian sales representatives also bought lunches for health care professionals, and those purchased lunches were a vehicle for Kadian Sales representatives to make sales presentations to certain doctors.¹⁴¹ As Hadland demonstrated, such gifts to doctors are directly correlated with their prescribing habits and their willingness to increase opioid prescribing.¹⁴² Kadian sales representatives were also instructed to detail pharmacists to pass along information and to “ensure that patients get [Co-Pay] coupons.”¹⁴³
- xxii. The effect of providing free or discounted addictive prescription drugs is seen in a December 2011 memorandum showing the impact of individualized attention by sales representative to doctors and pharmacists. The memo encouraged the sales rep to “continue to use your Kadian Co-Pay cards to gain access with your tough-to-see prescribers” and observed that a “great example of the impact you will have with your prescribers was your lunch with Dr. Zavarei in Anaheim. He was impressed that he now had a Kadian rep calling on him again. Your focus on the benefits of Kadian having a steady blood level through at 12 or 24 hour period was one that Dr. Zavarei easily bought into. He immediately mentioned he had patients that he would like to switch from generic MS Contin to Kadian”. The sales rep was also lauded for establishing a “great rapport” with a local pharmacist stocking the “Actavis generic version of Kadian” that “will pay dividends for Dr. Zavarei’s patients, and will make your new pharmacists contact at Ben’s Pharmacy extremely happy with his new business.”¹⁴⁴ According to Actavis’s own internal data, although Dr. Zavarei wrote no Kadian prescriptions in the year prior to being detailed, in January 2012, the month after the sales call, he wrote two

¹³⁹ California Killion deposition at 129:1-140:11; California Killion Deposition Ex. 10, Allergan_MDL_0026826 at 26868.

¹⁴⁰ See discussion of 2019 ASPPH report at § C.2.i.i., above, and §C.4.b.xxi., below.

¹⁴¹ California Killion deposition at 156:3-157:11.

¹⁴² See discussion of Hadland at §C.4.b.ii,

¹⁴³ California Killion deposition at 158:13-23.

¹⁴⁴ ALLERGAN_MDL_00396748 at -6749. Although this particular memorandum pertained to the Los Angeles area, it is likely that the same tactics had the same effect in Ohio and wherever else they were employed, since such tactics are employed for the purpose of increasing sales.

prescriptions for the Actavis generic version of Kadian,¹⁴⁵ making him one of the “top 10 increases in prescription by prescriber” in that sales territory.¹⁴⁶

- xxiii. Watson Pharma trained their sales people to promote Norco, a combination of the opioid hydrocodone and acetaminophen, by offering free product to doctors using the following language: “The outstanding offer is that Watson will send you 1 – 100 count bottle of each of these two [Norco] strengths at no charge,” with little or no information of risks of opioids, and no mention at all of the risks of misuse, addiction, and death.¹⁴⁷ (2001)
- xxiv. In January 2002 Norco/Maxidone¹⁴⁸ Stocking Program Guidelines offered a “free goods promotion” as part of a program to “blitz all independent and small chain accounts that have not purchased Norco and Maxidone.”¹⁴⁹ Sales representatives would receive \$50.00 sales credit for each order and were cautioned “Do not get into any type of discussion or dialog about efficacy or your opinions. Stick to the script. We are offering the pharmacist free product to put on their shelf so they can fill the Norco and Maxidone scripts. End of discussion.”¹⁵⁰
- xxv. A March 2001 Watson sales training binder for Norco and Maxidone falsely stated that “Although physical dependence is common in patients receiving opioids for pain, addiction is quite rare. There is essentially no evidence that adequate administration of opioids for pain produces addiction.”¹⁵¹ In fact, dependence is common in those who take opioids daily, and addiction affects up to one quarter of pain patients prescribed opioids. Further, in selling Norco, Watson instructed its sales force to use physician-directed sales tools including “leave-behind premiums – pens, pads, etc. and samples.”¹⁵²
- xxvi. Janssen used a similarly aggressive sales force and discount coupons to promote its opioid products. For example, Janssen deployed drug reps to target doctors directly to give away free fentanyl, an opioid that is 50 to 100 times more potent than heroin.¹⁵³ Janssen trained its sales

¹⁴⁵ ACTAVIS0673141

¹⁴⁶ ACTAVIS0791949

¹⁴⁷ ALLERGAN_MDL_03733190

¹⁴⁸ Maxidone was another hydrocodone/acetaminophen product.

¹⁴⁹ ALLERGAN_MDL_03733544 (emphasis in original)

¹⁵⁰ *Id.*, at 3545.

¹⁵¹ ALLERGAN_MDL_03255938 at 5962.

¹⁵² *Id.*, at 5985.

¹⁵³ MCKMDL00334317. These free 5-packs of Duragesic were intended to provide 3 days per patch, for 15 days total, of continuous fentanyl exposure, which were essentially certain to create a predictable proportion of fentanyl-dependent consumers. Well-accepted data show that “the likelihood of chronic opioid use increase[s] with each additional day of medication supplied starting with the third day, with the sharpest increases in chronic opioid use

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representatives to promote the free fentanyl patches to doctors, with language as follows:

- A. “Physicians may be more inclined to try Duragesic because patients are now able to ‘sample’ Duragesic free of charge.”¹⁵⁴
- B. “Sell the coupons like they are a third product and close for action. ‘Dr. Smith, do you feel that the Duragesic coupons will be helpful to you and your patients when you are ready to convert to a long acting, because they can try Duragesic for free?’”¹⁵⁵
- C. “Pull out one coupon from the pack and explain each section of the coupon Explain that one coupon is good for one free box of five patches, which is fifteen days of treatment. Remind the doctors that the coupon must be accompanied by a written prescription.”¹⁵⁶
- D. “Display the coupons in a prominent place for easy access and to help remind the doctors of the program. It is very important to explain to the staff that you will replenish their coupon supply every month. This is very important so the doctors do not save the coupons for special patients.”¹⁵⁷
- E. “Be very enthusiastic about the coupons! Make the physicians feel special because they are a part of only a select few that have the opportunity to participate in this coupon program.”¹⁵⁸
- F. “I respond [to the doctor expressing reservations] by saying, ‘I believe that a patient in true chronic pain will try anything that you prescribe for them, because all the [sic] they want is pain

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observed after the fifth and thirty-first day on therapy, a second prescription or refill, 700 morphine milligram equivalents cumulative dose, and an initial 10- or 30-day supply. ... *The rate of long-term use* was relatively low (6.0% on opioids 1 year later) for persons with at least 1 day of opioid therapy, but *increased to 13.5% for persons whose first episode of use was for ≥ 8 days* and to 29.9% when the first episode of use was for ≥ 31 days. Although ≥ 31 days of initial opioid prescriptions are not common, approximately 7% do exceed a 1-month supply.” Shah A, Hayes CJ, Martin BC. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use — United States, 2006–2015. *MMWR Morb Mortal Wkly Rep* 2017;66:265–269, at p. 269 and 267. DOI: <http://dx.doi.org/10.15585/mmwr.mm6610a1> (emphasis added) These data show that Janssen’s free 15-day supply of Duragesic undoubtedly increased the number of long-term users of opioids, thereby increasing the occurrence of dependence and the likelihood of OUD, despite the lack of reliable evidence of long-term benefit.

¹⁵⁴ JAN-TX-00066294.

¹⁵⁵ *Id.*

¹⁵⁶ *Id.*

¹⁵⁷ *Id.*

¹⁵⁸ *Id.* (emphasis in original)

relief. So, why not use a coupon that allows the patient to try Duragesic for free! You and the patient have nothing to lose.”¹⁵⁹

- xxvii. Janssen’s business and tactical plans reported successful promotion of Duragesic. Its 2001 business plan for Duragesic reported a strong positive correlation between the number of promotion calls to pain specialists and the number of new Duragesic prescriptions they wrote, and that increasing the number of calls from 1-2 in one quarter to 3-4 the next increased new Duragesic prescriptions by 14.3%.¹⁶⁰
- xxviii. Additionally, a 2005 Tactical Plan included review of Duragesic “e-detailing” and voucher programs which showed successful return on investment (ROI).¹⁶¹ The plan reports that Janssen had a 1.5:1 return on a \$250,000 investment in an “internet-based promotional initiative” which had the objective of increasing “share of voice with high deciled physicians by delivering multi-wave DURAGESIC promotional messages via the internet.”¹⁶²
- xxix. The voucher program was even more successful, showing a 29:1 ROI, or \$12.9 million return on a \$431,000 investment in a sample voucher program for “a box of 25 mcg or 50 mcg patches redeemed at a pharmacy for a free 15 day trial of Duragesic,” with the objective of initiating “trials of DURAGESIC immediately after short acting opioids earlier in the chronic pain treatment continuum for new patient starts.”¹⁶³
- xxx. In addition to Duragesic, Janssen aggressively promoted Nucynta (tapentadol). Janssen did this in part by telling sales representatives that the more the Nucynta they sold, the more money they would make. A 2009 Janssen sales incentive and compensation plan informed sales people that “any NUCYNTA TRx’s generated in Q2 will pay \$40/TRx.”¹⁶⁴
- xxxi. The above-described evidence makes it clear that promotion of opioids to prescribers and their staff is a highly effective strategy for increasing opioid sales. Given the inherently addictive potential of opioids and the current opioid epidemic, such promotional activities should not be allowed.
- xxxii. In February 2018, a news release announced that Purdue Pharma “cut its sales force in half and will stop promoting opioids to physicians, following widespread criticism of the ways that drugmakers market addictive

¹⁵⁹ *Id.* at 6295.

¹⁶⁰ JAN-MS-00310269 at *11-12 (produced natively).

¹⁶¹ JAN-MS-00310213 (produced natively)

¹⁶² *Id.*, at *53.

¹⁶³ *Id.*, at *55.

¹⁶⁴ JAN-TX-00004105, at *13 (produced natively)

painkillers.”¹⁶⁵ This decision on the part of Purdue Pharma was tacit acknowledgement of direct-to-physician/pharmacy marketing as a major driver of the opioid epidemic.

xxxiii. In 2019, the ASPPH recommended stopping marketing of opioid medications: “Along with revisions in opioid drug labeling to discourage long-term use, federal regulations must be changed to prohibit (or strictly limit) the marketing of opioids to physicians and health systems....”¹⁶⁶ I agree that the aggressive marketing of addictive drugs, as described above, was never appropriate, and particularly improper when based on false and misleading messages of safety and efficacy. Though long overdue, the ASPPH recommendations should be implemented going forward.

d. Key Opinion Leaders

- i. To encourage doctors to prescribe more opioids, opioid manufacturers promoted the careers of physicians who were sympathetic to their cause. They singled out vocal proponents of liberal opioid prescribing, especially for chronic pain conditions, and paid these physicians to promulgate the benefits and minimize the risks.¹⁶⁷
- ii. These ‘key opinion leaders’ and others, including the Defendant manufacturers, actively promoted a 1980 *New England Journal of Medicine* Letter to the Editor by Porter and Jick, entitled “Addiction Rare in Patients Treated with Narcotics.”¹⁶⁸ Porter and Jick described that among hospitalized patients taking opioids for pain, they found only four cases of addiction among 11,882 patients treated with opioids. This letter was used as evidence by Defendants and key opinion leaders to argue that opioid addiction is rare in the course of medical treatment, despite the fact that the so-called evidence was of poor quality and not representative of patients seen in usual clinical care. The catch phrase “less than 1% get addicted,” based on this one data point, was used in opioid manufacturers’ branded advertisements and other promotional materials. (See Appendix I on promotional material.)
- iii. Significantly, the population in question in the Porter and Jick article is described as “hospitalized,” and receiving at least one dose of an opioid, without any reference to the size of the dose or range or duration of exposure. There is no reasonable basis to compare the risk of addiction

¹⁶⁵ *OxyContin maker stops promoting opioids, cuts sales staff*, Reuters, February 10, 2018, <https://www.reuters.com/article/us-usa-opioids-purduepharma/oxycontin-maker-stops-promoting-opioids-cuts-sales-staff-idUSKBN1FU0YL>

¹⁶⁶ ASPPH, “Bringing Science to Bear”, fn.16, above, at p. 11.

¹⁶⁷ Saper JR. The Influence of Pharma and Device Manufacturers on APS and other PMAs: A War Within a War. (MDL No. 2804 Saper Dep. Ex. 6, at pp. 3-4).

¹⁶⁸ Porter J, Jick H. Addiction rare in patients treated with narcotics. *N Engl J Med*. 1980;302(2):123.

among hospitalized patients who may have received only a single dose or short-term course of opioid medication, with the far greater risk among patients prescribed opioids for non-cancer chronic pain outside the hospital setting. This is especially true in light of the well-known relationship between longer duration of opioid exposure and increased risk of dependence and abuse.

- A. Despite the lack of reasonable or scientific basis for using Porter and Jick to support the concept of the “rarity” of addiction, Defendants and their key opinion leaders frequently cited this letter to the editor as if it provided sound scientific support for wide prescribing of opioids.
- B. A 2017 study reported in the *New England Journal of Medicine* found that the Porter and Jick letter had been cited 608 times, compared to a median of 11 citations to other letters published contemporaneously.¹⁶⁹ The authors stated: “In conclusion, we found that a five-sentence letter published in the Journal in 1980 was heavily and uncritically cited as evidence that addiction was rare with long-term opioid therapy. We believe that this citation pattern contributed to the North American opioid crisis by helping to shape a narrative that allayed prescribers’ concerns about the risk of addiction associated with long-term opioid therapy. In 2007, the manufacturer of OxyContin and three senior executives pleaded guilty to federal criminal charges that they misled regulators, doctors, and patients about the risk of addiction associated with the drug. Our findings highlight the potential consequences of inaccurate citation and underscore the need for diligence when citing previously published studies.”¹⁷⁰
- C. The following are examples of opioid manufacturer-sponsored, inappropriate and misleading reliance upon the Porter and Jick letter: (i) In 1996, a Purdue Frederick-funded study reported that: “In three studies involving almost 25,000 patients without a history of drug dependence, there were only 7 cases of iatrogenic addiction.”¹⁷¹ (Citing Porter and Jick and 2 other inapplicable studies by Perry and Medina, discussed in this Report at Section §C.4.d. iv-v, below). Moulin *et al.* described the risk of addiction as “negligible.”¹⁷² Purdue Frederick is listed as a grant supporter

¹⁶⁹ Leung PTM, *et al.* A 1980 Letter on the Risk of Opioid Addiction. *N Engl J Med.* 2017; 376:2194-2195, at p. 2194

¹⁷⁰ *Id.*, at pp. 2194-2195.

¹⁷¹ Moulin DE *et al.* Randomised trial of oral morphine for chronic non-cancer pain. *Lancet.* 1996;347:143-147, at p. 143.

¹⁷² *Id.*, at p. 147.

of the Moulin article.¹⁷³ (ii) In 1997, Purdue published “I Got My Life Back” a brochure and video promoting a “*less than 1%*” addiction rate, citing to Porter and Jick (1980);¹⁷⁴ (iii) In 1998, a Janssen-funded study reported that a “*low risk* of iatrogenic psychological dependence has been observed in patients without a history of substance abuse” citing to Porter and Jick (1980);¹⁷⁵ (iv) A 2001 Janssen presentation, “Optimizing Chronic Pain Management with Duragesic,” cites Porter and Jick (1980) for “low” risk of addiction in non-addicts and states that “the potential for addiction is in the patient, not the opioid.”;¹⁷⁶ (v) In 2001, an Endo-sponsored KOL (Dr. Covington, Cleveland Clinic) presentation and handout titled “Opioid maintenance in chronic non-malignant pain” concluded that “Iatrogenic addiction in treatment of acute pain is *virtually nonexistent*” citing to Porter and Jick (1980);¹⁷⁷ (vi) In 2002, a Cephalon annual sales meeting presentation entitled, “The Myth of Addiction” concluded there was a “*0.06% chance of becoming addicted*” citing to Porter and Jick,¹⁷⁸ and directed its sales force: “Never Refer to Addiction when talking about opioids – especially Actiq!”¹⁷⁹ These examples demonstrate the point made in the 2017 *NEJM* article, that the Porter and Jick Letter was “heavily and uncritically cited as evidence that addiction was rare with long-term opioid therapy,” and “contributed to the North American opioid crisis by helping to shape a narrative that allayed prescribers’ concerns about the risk of addiction associated with long-term opioid therapy.”¹⁸⁰

- iv. Other articles cited by key opinion leaders and Defendants on low addiction rates in pain patient populations, included a national survey of burn facility staff with knowledge of >10,000 burn patients administered opioids, with no cases of iatrogenic addiction identified.¹⁸¹ Burn debridement, consisting of the removal of dead tissue to promote healing, is a procedure carried out in a hospital setting. Mean administered morphine during the procedure was only 8.9 mg, a very low dose. Although the authors referred to continued narcotic therapy after

¹⁷³ *Id.*

¹⁷⁴ PKY183063227 (brochure); PPLPC009000022561 (video transcript) (emphasis added)

¹⁷⁵ Dellemijn PLI, *et. al.* Prolonged treatment with transdermal fentanyl in neuropathic pain. *Journal of Pain and Symptom Management*. 1998;16(4):220-229, at pp. 227-228. (emphasis added)

¹⁷⁶ JAN-MS-00653403 (December 14, 2001), at *66 (produced natively).

¹⁷⁷ ENDO-OPIOID_MDL-02002494; ENDO-OPIOID_MDL-02002495 at slides 4-5 (emphasis added)

¹⁷⁸ TEVA_AAMD_00791885 at 1901-1902 (emphasis added)

¹⁷⁹ TEVA_AAMD_00791885 at 1887

¹⁸⁰ Leung, “A 1980 Letter”, fn. 169, above, at p. 2194.

¹⁸¹ Perry S, Heidrich G. Management of pain during debridement: A survey of U.S. burn units. *Pain*. 1982;13(3):267-280, at 267-77.

debridement, no details were provided regarding dose or duration, and burn healing is inherently a time-limited process unlike chronic arthritis, back pain, or other conditions for which Defendants promoted opioid therapy. As in the case of the Porter and Jick letter, the low risk of addiction for a short-term, hospital-based procedure and its limited sequelae are not comparable to the significant risk of addiction with long-term opioid therapy for chronic pain, and it is misleading to cite the burn study to support a claim of low addiction risk of opioids. Further, the study was not *a priori* designed to study addiction outcomes and did not use rigorous methodology to study this outcome.

- v. Opioid manufacturers and their key opinion leaders also cited a survey study of a large headache clinic by Medina, *et al.*, in support of the claim that risk of addiction was low.¹⁸² Sixty-two patients fulfilled criteria for inclusion in the study, in that they had been prescribed either a narcotic (codeine or propoxyphene), or a barbiturate (butalbital) or both. Thirty-eight of the 62 patients were treated with butalbital, a Schedule III medication in the class of barbiturates, and six were treated with propoxyphene (Darvon), a Class IV drug. The authors reported, “Eight were dependent; six physically addicted, two psychologically dependent and two were abusers There is danger of dependency and abuse in patients with chronic headaches.” Reliance upon the Medina study to suggest absence of risk appears to contradict the interpretation of the data by the authors themselves, who explicitly acknowledged the dangers. The authors also used conflated definitions of dependence, addiction, and ‘abuse’ not consistent with other studies or with DSM criteria of any edition; however, the finding that two patients were “psychologically dependent” would generally have been considered equivalent to a diagnosis of “addiction” at the time of the Medina article. In addition, the study did not use objective criteria for tracking misuse, such as urine toxicology or collateral information from family or the prescription drug monitoring database, which would have increased the investigators’ likelihood of identifying aberrant behavior.
- vi. Dr. Russell Portenoy, former chairman of the Department of Pain Medicine and Palliative Care at Beth Israel Medical Center in New York City, was a key opinion leader for opioid manufacturers. Between 1997 and 2012, Dr. Portenoy received nearly \$29,000 in direct payments from Janssen and its parent Johnson & Johnson (J&J), including \$16,940 for “sponsored research”.¹⁸³ Dr. Portenoy spread his pro-opioid messages as President of the American Pain Society, and as a member of the boards of the American Pain Foundation and the American Pain Society,

¹⁸² Medina JL, Diamond S. Drug Dependency in Patients with Chronic Headaches. *Headache J Head Face Pain*. 1977;17(1):12-14. doi:10.1111/j.1526-4610.1977.hed1701012.x, at pp. 1-2.

¹⁸³ JAN-MS-00000001 at 0008.

organizations that received funding from the Pharmaceutical Opioid Industry.¹⁸⁴ The many hundreds of thousands of dollars in Pharmaceutical Opioid Industry payments to individuals such as Dr. Portenoy are evidence of Industry support for “key opinion leaders” whose work was used by the Industry to encourage opioid prescribing through aggressive misrepresentation of risks and benefits.¹⁸⁵

- A. In 1986, Drs. Russell Portenoy and Kathleen Foley published a retrospective case series of 38 patients with chronic pain.¹⁸⁶ Portenoy and Foley’s review does not constitute a high level of scientific evidence. It did not include a large number of patients.¹⁸⁷ There was no comparison group taking a placebo or getting some other treatment for pain, such as physical therapy or non-opioid medication.¹⁸⁸ It was retrospective rather than prospective, meaning the authors asked patients to recollect past experiences, biased by recall effects, rather than soliciting their reactions going forward in real time. Nonetheless, they concluded “opioid maintenance therapy initiated for the treatment of chronic non-malignant pain can be safely and often effectively continued for long periods of time.”¹⁸⁹ The statement represented a departure from previous practice, in which opioids were used almost exclusively for acute (after surgery or injury) and palliative pain (at the end of life). Portenoy and Foley went on to say that their review suggested that opioid medications can be used in this manner “with relatively little risk of producing the maladaptive behaviors which define opioid abuse.”¹⁹⁰ Yet in the 19 patients they “reviewed in detail,” one developed “psychological deterioration” and was hospitalized, where “opioid intake was rapidly increased without medical approval,” and the other appeared to be diverting prescribed opioids: “the patient appeared to require high doses of methadone for pain relief. After several months, a plasma methadone level revealed

¹⁸⁴ Declaration of Russell K. Portenoy, M.D. in MDL 2804, at ¶ 37-40.

¹⁸⁵ Senate Homeland Security and Gov Affairs Comm, 116th Cong., Report on Fueling an Epidemic Report Two: Exposing the Financial Ties Between Opioid Manufacturers and Third Party Advocacy Groups (2018) at pp. 10-11, <https://www.hsgac.senate.gov/imo/media/doc/REPORT-Fueling%20an%20Epidemic-Exposing%20the%20Financial%20Ties%20Between%20Opioid%20Manufacturers%20and%20Third%20Party%20Advocacy%20Groups.pdf>.

¹⁸⁶ Portenoy RK, Foley KM, Chronic Use of Opioid Analgesics in Non-Malignant Pain: report of 38 cases. *Pain*. 1986;25:171-186.

¹⁸⁷ *Id.*, at pp. 172-173. Patients reviewed were derived from two separate studies and only 19 patients were under treatment at the time of the study.

¹⁸⁸ *Id.*

¹⁸⁹ *Id.*, at p. 178.

¹⁹⁰ *Id.*, at p. 184.

almost no circulating drug.”¹⁹¹ The authors ignored these adverse outcomes when they stated, “There were no episodes of clinically significant adverse effects from the use of opioids.”¹⁹²

- B. Portenoy’s co-author Foley stated in a subsequent 2011 letter to the editor, “We disagree with the concept of setting a maximum dose. The pharmacology of opioid use in the treatment of pain is based on dose titration to effect.”¹⁹³ This statement encouraged the practice of increasing the dose of opioids over time as tolerance developed. I have seen scores of patients over the years on very high doses of opioids, some as high as 2,000 morphine milligram equivalents per day (MED), putting them at high risk for opioid-related morbidity and mortality. Meanwhile, there is no reliable evidence to support the use of higher doses of opioids, and mounting evidence that risks of opioids are directly related to dose and duration: the higher the dose, and the longer patients are on them, the higher the risk.
- C. Edlund *et al.* state, “Clinicians should be aware that as they proceed from acute to chronic opioid therapy, the evidence of efficacy decreases whereas the opioid use disorder (OUD) risk increases substantially.”¹⁹⁴ The odds of developing an OUD in those exposed to opioids for 90 days or more, compared to those not exposed (odds ratio), are as follows: For low dose (1-36 MMEs per day), the odds ratio was 14.92 (95% CI = 10.38, 21.46); for medium dose (36-120 MMEs per day) the odds ratio was 28.69 (95% CI = 20.02, 41.13); for high dose (> 120 MMEs per day) the odds ratio was 122.45 (95% CI = 72.79, 205.99).¹⁹⁵ Another way to say this is that patients exposed to 120 MMEs of opioids for 90 days or more, were 122 times more likely to develop an opioid use disorder within the year than those not exposed to opioids.
- D. These data from the Edlund study show that both dose and duration affect the risk of opioid use disorder. That is, the higher the dose, the greater the risk; and the longer the duration of exposure, the greater the risk. When both higher dose and longer duration are found, patients are 120 times more likely to suffer

¹⁹¹ *Id.*, at p. 177.

¹⁹² *Id.*

¹⁹³ Foley KM, Fins JJ, Inturrisi CE. A true believer’s flawed analysis. *Arch Intern Med.* 2011. doi:10.1001/archinternmed.2011.166, at p. 867.

¹⁹⁴ Edlund, *et al.*, “Role of Opioid Prescription,” fn.76, above, at p. 561,

¹⁹⁵ *Id.* at p. 559-60. As shown in Table 3 at p.561, based on Edlund’s data, the OR with increasing dose and duration is far greater than the OR for other factors, such as prior substance use disorders or psychiatric diagnoses.

from opioid use disorder than patients who were not prescribed opioids.

- E. In 2011, Dr. Portenoy conceded that there was no reliable evidence to support the statement that opioids are ‘low risk.’ In a taped interview Dr. Portenoy described his promotion of opioids in the 1990s and early 2000s as follows: “I gave so many lectures to primary care audiences in which the Porter and Jick article¹⁹⁶ was just one piece of data that I would then cite. I would cite 6 to 7 maybe 10 different avenues of thought or evidence, *none of which represents real evidence*. And yet what I was trying to do was to create a narrative so that the primary care audience would look at this information *in toto* and feel more comfortable about opioids in a way they hadn’t before. . . . Because the primary goal was to de-stigmatize, *we often left evidence behind*.”¹⁹⁷ (emphasis added). Dr. Portenoy’s statement supports my opinion that there was no reliable evidence that opioids are low risk.

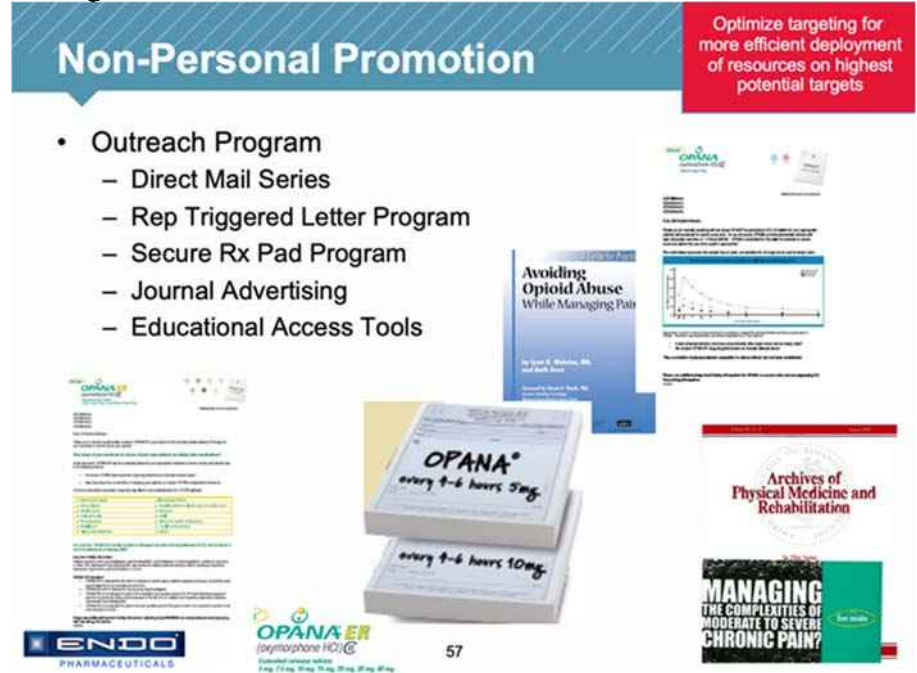
■ Dr. Lynn Webster, a key opinion leader and paid consultant for the opioid manufacturing defendants, wrote a book called “Avoiding Opioid Abuse While Managing Pain.” This book was used by Endo to promote increased sales of Opana by distributing it to physicians and pharmacies, including Discount Drug Mart, in the Cleveland Ohio area.¹⁹⁸

¹⁹⁶ Porter, Jick, *et al.*, “Addiction Rare,” fn. 168, above.

¹⁹⁷ Lurie J., *Doctors Receive Opioid Training. Big Pharma Funds It. What Could Go Wrong?* Mother Jones. <https://www.motherjones.com/politics/2018/04/doctors-are-required-to-receive-opioid-training-big-pharma-funds-it-what-could-go-wrong/>.

¹⁹⁸ END00666533.

- A. Webster's book was featured in Endo's "2009 OPANA Brand Strategic Plan," as shown below.¹⁹⁹



- B. Webster's book contains many of the misleading messages about opioids that contributed to the oversupply, including that opioids are evidence-based treatment for chronic pain (they are not), and that addiction is rare (it is not) in individuals treated by a doctor with opioids for chronic pain.²⁰⁰ In reality, every one of the following statements in the Webster book is false, misleading, unsupported by, or directly contradicted by scientific evidence:

- I. "In a world with few alternatives, opioids remain the best treatment available for many chronic pain conditions and are the first choice of therapy for acute and postoperative pain."²⁰¹ Opioids are not evidence-based treatment for chronic pain, and in fact work no better than Tylenol while incurring many more risks to the individual and the public health. Although opioids do work short term for acute pain, they are not always the "first choice of therapy" for acute or postoperative pain. Some individuals don't tolerate

¹⁹⁹ ENDO-CHI_LIT-00023217 (produced natively), at *57. Alongside Webster's book, note the many other methods Endo used to target prescribers: "Direct Mail Series," "Rep Triggered Letter Program," "Secure Rx Pad Program" (branded with the company's opioid products, in this case "OPANA"), "Journal Advertising," and "Educational Access Tools" (such as the sad-face/happy-face Pain Evaluator used by Endo and described below at §4.e.vi.).

²⁰⁰ Webster, Lynn. *Avoiding Opioid Abuse While Managing Pain*. Sunrise River Press, 2007, see ENDO-CHI_LIT-00538705, at -8725.

²⁰¹ *Id.*, at -8713.

opioids, even short term, and even short term exposure increases the risk of persistent and addictive use. In fact, recent research has determined that opioid-sparing protocols provide equivalent pain relief and fewer risks with non-opioid analgesics.²⁰²

- II. “Opioids offer safe, effective treatment for many chronic pain conditions and pose little risk of addiction for most patients who take them to control pain.”²⁰³ As above, this statement is false. Opioids are neither safe nor effective for chronic pain and pose significant risk of addiction and overdose death.
- III. “Addiction can usually be predicted.”²⁰⁴ Not true. There is no way to tell who will and will not become addicted to opioids through a doctor’s prescription. Risk factors like family or personal history of mental illness incur less risk than simple exposure to opioids at high doses for long duration (three months or greater).²⁰⁵ Further, the Opioid Risk Tool, created by Dr. Webster and widely used and promoted to screen out patients vulnerable to addiction, has been shown in follow up studies to be “no better than chance” at predicting who will become addicted to opioids in the course of pain treatment.²⁰⁶
- IV. “When physicians agree to perform surgery but then refuse to treat postoperative pain, their fear of prescribing opioids has become exaggerated. The refusal to adequately relieve postsurgical pain is unconscionable.”²⁰⁷ This statement falsely conflates relieving post-surgical pain with prescribing opioids. Non-opioids work just as well or better than opioids in many instances of acute pain. Further, perioperative opioids for acute pain have become a major gateway to persistent opioid use and opioid use disorder.²⁰⁸
- V. “As a hallmark of the increasing acceptance of analgesics used to control pain, a 1997 consensus document published

²⁰² Discussed below at Section §C.15.b and Appendix IV.

²⁰³ ENDO-CHI_LIT-00538705, at -8713.

²⁰⁴ *Id.*, at -8717.

²⁰⁵ Discussed above at Section §C.8.r.

²⁰⁶ Clark MR, Hurley RW, Adams MCB. Re-assessing the Validity of the Opioid Risk Tool in a Tertiary Academic Pain Management Center Population. *Pain Med.* 2018;19(7):1382-1395. <http://dx.doi.org/10.1093/pm/pnx332>, at p. 1382.

²⁰⁷ ENDO-CHI_LIT-00538705, at -8717. *See* discussion of opioid overprescribing after surgery, below, at Section §C.10.q

²⁰⁸ As discussed below in Section §C.10.q.

by the American Academy of Pain Medicine and the American Pain Society advised all types of clinicians (not just specialists) to consider the use of opioids in selected patients for the management of chronic nonmalignant pain.”²⁰⁹ The AAOM and APS consensus document was funded by industry, scientifically inaccurate, and ultimately discredited.

- C. Dr. Lynn Webster’s own Curriculum Vitae reports that he was on the American Academy of Pain Medicine (AAPM) Board of Directors from 2007 through at least 2016, president-elect/president of the AAPM from February 2012 to March 2014, Director-at-large of the AAPM from 2008-2010, and Treasurer from 2010-2011 (also chairing finance and fundraising committees).²¹⁰ Findings from a U.S. Senate Finance Committee investigation of opioid manufacturers’ financial relationships with patient advocacy groups and other entities reported payments by various opioid manufactures to the AAPM during this time 2007-2016 period including \$858,320 from Endo, \$172,525 from Janssen/Johnson & Johnson, \$1,359,715 from Purdue, and \$ 1,022,675 from Teva/Cephalon.²¹¹ Also, Dr. Webster was program chair for AAPM CME programs on opioid prescribing that were funded by opioid manufacturers including Endo, Mallinckrodt and Purdue.²¹²
- D. On one of his CVs, Dr. Webster disclosed that he worked as a consultant for Cephalon and on advisory boards for Alpharma, Cephalon, Purdue and others.²¹³ On a 2005 Clinical Investigator Financial Disclosure form, Dr. Webster reported that he received a total \$17,200 from Cephalon in 2004 “for speaking.”²¹⁴ In 2008, Dr. Webster signed a 3 year consulting agreement with Purdue.²¹⁵ Also, in 2011, Cephalon contracted with Dr. Webster to serve as a consultant on Cephalon’s Pain Franchise Medical Scientific Advisory Board, for \$4,500 for 1.5 days work.²¹⁶ In

²⁰⁹ *Id.*, at -8725.

²¹⁰ ENDO-OPIOID_MDL-03699994, at -9996.

²¹¹ United States Senate Committee on Finance, Findings from the Investigation of Opioid Manufacturers’ Financial Relationships with Patient Advocacy Groups and other Tax-Exempt Entities (December 16, 2020) <https://www.finance.senate.gov/imo/media/doc/2020-12-16%20Finance%20Committee%20Bipartisan%20Opioids%20Report.pdf>. at Appendices A-B

²¹² ENDO-OPIOID_MDL-04066791, at -6797 and -6800.

²¹³ ENDO-OPIOID_MDL-00307222, at -7224-7225.

²¹⁴ TEVA_AAMD 00629997

²¹⁵ PPLP003478494

²¹⁶ TEVA_MDL_A_07249903

2016, Teva also contracted Dr. Webster to serve as a Medical Expert Consultant for Vantrela ER at \$500 an hour.²¹⁷

■ The Pharmaceutical Opioid Industry continues to spend significant amounts of money to promote their products, including payments for “consulting” relationships with influential doctors and educators. An analysis of CMS Open Payment data for non-research payments by companies marketing opioids to teaching hospitals from 2013-2018 found that “[o]verall, there were 444 payments linked to opioid products totaling \$7,023,140 (median value of individual payment \$1348; IQR \$245 to \$20,291)... In addition to payments linked to opioids, we identified 5,168 payments made by 22 companies marketing opioids which were not linked to any opioid or non-opioid product; the total value of these payments was \$120.0 million.”²¹⁸ Of the \$7 million linked to specific opioid products, \$3.7 million of that was for “consulting fees”.²¹⁹ The products promoted at teaching hospitals include Endo’s Opana, Purdue’s OxyContin, Hysingla, and Butrans, and Janssen’s Nucynta.²²⁰

e. Medical School Curricula

- i. In 2003, Purdue entered into an agreement with Harvard Medical School that provided for a significant financial contribution from Purdue to Harvard, as well as a cooperative arrangement between the two entities in developing curriculum and materials for instruction about pain management. In particular, Attachment B to the Agreement provides that (i) “Purdue Pharma shall be encouraged to suggest ideas for areas where education in the field of pain is needed, and for curriculum which might meet such needs”; (ii) “Purdue Pharma shall be encouraged to suggest ideas for CME [Continuing Medical Education] courses”; and (iii) with respect to the goals of the educational program, “Purdue Pharma shall be encouraged to make suggestions concerning such courses and materials.”²²¹
- ii. In 1999, Purdue Pharma funded the new Pain Research, Education and Policy (PREP) program at Tufts University School of Medicine, contributing more than \$2 million to the venture over the next 10 years.²²² In addition to monetary gifts, a Purdue representative sat on the PREP

²¹⁷ TEVA_MDL_A_06746958, at -6967.

²¹⁸ Anderson TS et al. Financial payments to teaching hospitals by companies marketing opioids. *J. General Internal Medicine* (2019), at p. 1.

²¹⁹ *Id.* at Table 2.

²²⁰ *Id.* at Table 1.

²²¹ PPLPC021000425373, at Appendix B. The industry also made substantial contributions to the University of Wisconsin - Madison School of Medicine, see discussion at §4 h.xi., below.

²²² Caleb Symons, Austin Clementi, *Report reveals loose conflict-of-interest policies, deference to donors benefitted Purdue Pharma*, The Tufts Daily, Dec. 6, 2019. <https://tuftsdaily.com/news/2019/12/06/sackler-report-reveals-lack-due-diligence-tufts/>, at p. 1.

steering committee, a privilege that included the opportunity to influence the medical school curriculum and encourage preferred research.²²³ Purdue gave \$380,000 for Tufts' Center for the Study of Drug Development (CSDD), which conducted research for pharmaceutical companies, regulators, and policymakers.²²⁴ Purdue also funded the Comprehensive Educational Program (CEP) to host projects in the interest of both Tufts and Purdue.²²⁵

- iii. David Haddox, a senior executive of and Key Opinion Leader for Purdue (and co-author of the article that inspired the misleading concept of “pseudoaddiction” discussed in more detail at Section §C.4.k) was appointed an adjunct faculty member and regular lecturer in Tufts PREP program until 2018.²²⁶ According to a detailed analysis of Tufts relationship with Purdue, including classes taught by Haddox, the report found that Haddox did not address opioid use disorder in his lectures on opioids and analogized “regulation of opioids to Prohibition.”²²⁷
- iv. Daniel Carr, Tufts University School of Medicine Professor of Public Health and Community Medicine and vocal advocate for chronic pain treatment with opioids, became director of PREP and testified to the FDA in 2002 as Purdue's consultant.²²⁸ He defended Purdue's role in the opioid crisis and was a vocal critic of “opioidphobia” which he defined as an irrational fear of prescribing opioids for chronic pain.²²⁹ Richard Sackler, president of Purdue from 1999 to 2003, was a member of Tufts University School of Medicine Board of Advisors for almost 20 years until his resignation in 2017.²³⁰
- v. Since 1980, Tufts University School of Medicine has accepted approximately \$15 million from Purdue and the Sackler family.²³¹ By 2019, Tufts Board of Trustees had reconsidered its relationship with Purdue and the Sackler family, removed the Sackler name from all buildings on its Boston Health Sciences Campus, and established a \$3 million endowment to prevent and treat substance use disorders.²³²
- vi. The Pharmaceutical Opioid Industry seeded the very foundation of evidence-based medicine, the peer-reviewed medical literature, by promoting studies that supported use of opioids for chronic pain based on

²²³ *Id.*, at p. 2.

²²⁴ *Id.*

²²⁵ *Id.*

²²⁶ *Id.*

²²⁷ *Id.*, at p. 5.

²²⁸ *Id.*, at pp. 2-3.

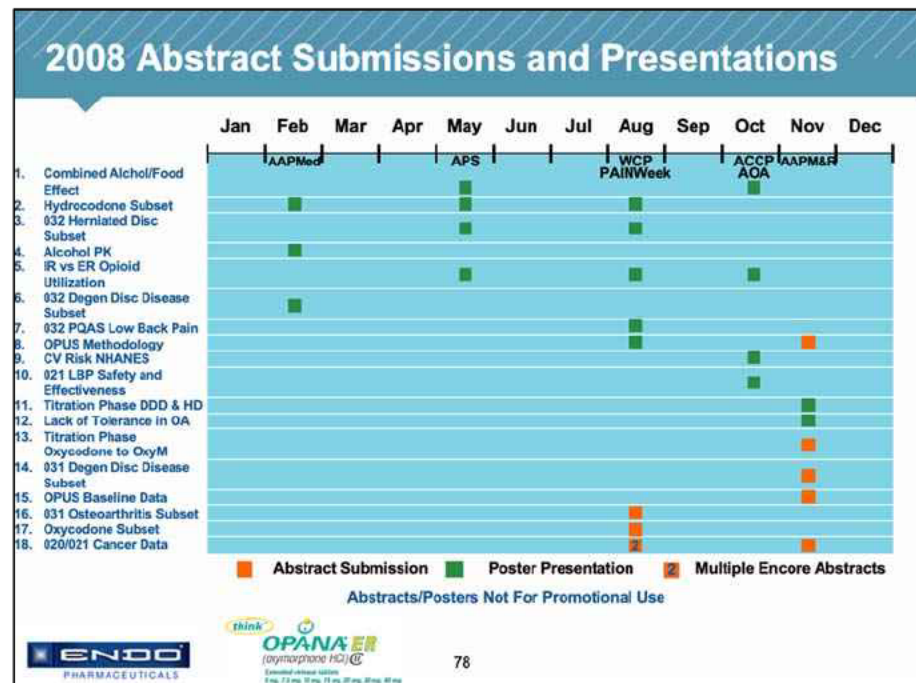
²²⁹ *Id.*, at p. 6.

²³⁰ *Id.*, at p. 3.

²³¹ *Id.*, at p. 2.

²³² *Id.*, at p. 7.

misleading evidence. A common practice was the use of studies showing *short term* benefit of opioids (12 weeks or less) in patients with chronic pain (pain everyday for 3 months or more); which is different than studies showing *long-term* benefit of opioids in patients with chronic pain, a subtle but crucial distinction. Endo's 2008 campaign to promote Opana for chronic pain funded and tracked 18 abstracts and presentations for 2008,²³³ including the following 12-week studies promoting opioids for chronic pain:²³⁴



- A. For example, a 12-week study reported that patients with “chronic low back pain” experienced “effective and durable analgesia” with Opana ER. The study is misleading in that it implies Opana ER is beneficial for chronic pain, based on a study of short-term use. It also promotes safety of Opana ER in a misleading manner by reporting no serious adverse effects, without disclosing that the risks of the most serious adverse effects of OUD and mortality increase with dose and duration of exposure, and that the dose is often increased over time due to

²³³ Nine of the eighteen studies were co-authored by Endo employees (Harry Ahdieh, R. A. Puenpatom).

²³⁴ ENDO-CHI_LIT-00023217, at *78 (produced natively). See ENDO-OPIOID_MDL-06656285 (Opana ER tab) Endo-supported abstracts were submitted and/or presented at conventions or conferences for the American Academy of Pain Medicine, American Pain Society, International Association for the Study of Pain – World Congress on Pain, PAINWeek, American Osteopathic Association, American College of Clinical Pharmacy, and the American Academy of Physical Medicine & Rehabilitation. ENDO-OPIOID_MDL-06825188 at 191-192.

the phenomenon of tolerance, that is, a greater dose is required to achieve the same degree of pain relief.²³⁵

- B. A study by Gammaitoni et al was titled “Opana ER improves pain quality measures in opioid-experienced patients with chronic low back pain,” implying that it worked for chronic pain. Not true. The study itself was only 12 weeks long and inappropriately used to promote Opana for chronic pain.²³⁶
- C. Podolsky et al did a randomized clinical trial of the safety and efficacy of oxymorphone extended release for degenerative disc disease in opioid-naïve patients. This abstract begins with the scientifically invalid assertion, “It was previously demonstrated that oxymorphone extended release (OPANA ER) is safe and effective for treating chronic low back pain in opioid-naïve patients.” The abstract then made similar claims that Opana ER is “efficacious” for patients with chronic degenerative disc disease, based on another 12 week study. Notably, on the same page of the same set of conference abstracts, authors sponsored by Johnson and Johnson made essentially identical, misleading claims of efficacy of its tapentadol opioid product for chronic back pain, attesting to the widespread use of inadequate short-term studies to claim long-term safety and efficacy.²³⁷

vii. I also personally experienced the influence of the pharmaceutical industry on the curriculum during my own medical education in the 1990s. Our pain curriculum emphasized opioids as a safe and effective first-line treatment for all types of pain, including chronic pain; failed to provide information on the risks of misuse, addiction, dependence, and overdose; provided no information on how to monitor for misuse/addiction or taper patients off of opioids when harms outweighed benefits; and suggested that physicians who refused opioids to patients in pain were lacking in integrity and compassion.

f. Continuing Medical Education.

- i. The practicing physician relies on continuing medical education (CME) conferences to acquire state of the art knowledge about the latest scientific evidence in medical practice. The average clinician busy seeing patients

²³⁵ Hale, Martin & Ma, Tasneem & Ahdieh, H. & Kerwin, R.. Efficacy of oxymorphone extended release in opioid-experienced patients with chronic low back pain due to a herniated disc: Subgroup analysis of a randomized, double-blind, placebo-controlled trial. *Journal of Pain*. 2008;9. 40-40. 10.1016/j.jpain.2008.01.180.

²³⁶ Gammaitoni A, Gould E, Ahdieh H, et al. Opana ER improves pain quality measures in opioid-experienced patients with chronic low back pain. *Journal of Pain*. 2007;8(4):S440

²³⁷ Podolsky G, Ahdieh H, Ma T, Gould E. Randomized clinical trial of the safety and efficacy of oxymorphone extended release for degenerative disc disease in opioid-naïve patients. *Journal of Pain*. 2009.

cannot wade through the voluminous literature him or herself. Instead, (s)he attends CME conferences, and assumes that the knowledge disseminated there, especially by esteemed academic colleagues, represents unbiased research. The FDA hires independent auditors to review CME courses to make sure they're following a blueprint and are free of pharmaceutical influence, but auditors are required to audit no more than 10% of all CME.²³⁸

- ii. Drug company-sponsored continuing medical education (CME) preferentially highlights the sponsor's drug(s) compared with other CME programs. The average physician attending CME courses underestimates the influence of industry-sponsored speakers and industry-sponsored CME, which is considerable. Data show changes in prescriber practice in favor of the sponsor's drug, after participation in an industry sponsored CME event.²³⁹
- iii. Not only has drug-company involvement in continuing medical education programs become prolific generally over the past several decades, but Defendants employed CME as part of the strategy to deploy their message about opioids starting in the late 1990s and continuing to today.²⁴⁰
- iv. The use of "Speakers Bureaus" of doctors, trained by a drug company to promote its product, is an adjunct to the CME strategy. "From 1996 to 2001, Purdue conducted more than 40 national pain-management and speaker-training conferences at resorts in Florida, Arizona and California. More than 5000 physicians, pharmacists, and nurses attended these all-expenses paid symposia, where they were recruited and trained for Purdue's national speaker bureau. It is well-documented that this type of pharmaceutical company symposium influences physicians' prescribing, even though the physicians who attend such symposia believe that such enticements do not alter their prescribing patterns."²⁴¹
- v. Endo budgeted more than \$7 million for Promotional Speaker Programs, out of a total annual budget of \$15.8 million dollars, to promote Opana in 2009,²⁴² describing the importance of their plan through the promotional effort as follows: "Key to OPANA ER's Growth in 2008 is the Completion of Over 720 Promotional Speaker Programs in the 1st Half,"²⁴³ and "Positive ROI for OPANA Promotional Speaker Programs," showing

²³⁸ Lurie, "Doctors Receive Opioid Training", fn. 197, above, at p. 3.

²³⁹ Wazana A. Physicians and the pharmaceutical industry: Is a gift ever just a gift? *JAMA*. 2000;283(3):373-380. <http://dx.doi.org/10.1001/jama.283.3.373>, at pp. 373, 377-78.

²⁴⁰ Saper, "The Influence of Pharma," fn. 167, above, at p. 2.

²⁴¹ Van Zee, "The Promotion and Marketing of OxyContin", fn. 94, above, at pp.221-22.

²⁴² ENDO-CHI_LIT-00023217, at *81 (produced natively).

²⁴³ *Id.*, at *19.

nearly 200% ROI by 28 weeks.²⁴⁴ The objective was to “grow OPANA ER market share by 1%” with TRx of 640,000 and net sales of OPANA ER at \$190 million.²⁴⁵

- vi. Teva/Cephalon Pharmaceutical’s “2005 ACTIQ Marketing Plan” tactical summary of sales strategies clearly delineate how they planned to use misleading marketing messages in the form of “continuing medical education” to promote their products, including their branded-fentanyl product “Actiq.” Teva/Cephalon’s strategy focused on persuading doctors of the need for ACTIQ as a supplement to chronic opioid therapy, to treat so-called “Breakthrough Pain,” (BTP) when in fact such patients likely sought greater doses of opioids because they had experienced “tolerance,” that is, they needed greater amounts of opioids to get the same degree of pain relief. See excerpted quotes below which describe Teva/Cephalon’s CME plan:
 - A. “ACTIQ marketing strategies will be executed through a variety of tactical initiatives that convey ACTIQ key messages and differentiate ACTIQ from its competitors based on its primary patient benefit, rapid onset of analgesia and pain relief.... Both promotional and continuing medical education programs will be implemented in 2005 and will continue to comprise a critical component of the tactical plan. New in 2005 is *Emerging Solutions in Pain (ESP)* which is an initiative developed by physicians for physicians, pharmacists and other healthcare professionals, to address some of the most critical issues in pain management today.”²⁴⁶
 - B. “Continuing Medical Education CME played a vital role in the education of physicians, nurses and pharmacists in 2004 regarding chronic cancer pain and non-cancer pain and Abuse, Addiction and Diversion. The major CME initiatives in 2004 included a CME on-demand teleconference, local and regional CME symposia (CEP Lectures), a tri-mesterly newsletter entitled *Emerging Solutions in Pain*, a repository website by the same name *EmergingSolutionsinPain.com*, sponsorship of the Pharmacologic Management of Pain Resource Center on Medscape and the sponsorship of the Breakthrough Cancer Pain category on *pain.com*, the most popular pain website on the internet. Additional CME initiatives included a CME insert in CME-TODAY for Primary Care Physicians and CME Symposia

²⁴⁴ *Id.*, at *20.

²⁴⁵ *Id.*, at *33.

²⁴⁶ TEVA_CAOC_00759630 at -9634.

at the annual congresses for AAPM, AAPM&R and the Northeast PRJ-MED .”²⁴⁷

- C. “The local and regional CME Symposia represented one of the most significant educational efforts in the area of pain management in 2004. These symposia allowed for the scientific exchange of extensive information on diagnosis, assessment and management of various pain related issues. Approximately 214 of these programs are expected to be completed by year end.”²⁴⁸
- D. “The tri-annual newsletter, Emerging Solutions in Pain, currently has a circulation of over 11,000 clinicians (8,000+ physicians and 2000+ nurses). The newsletter allows for communication of information on diagnosis and management of various pain types, in two distinct media: written and CD-ROM. The accompanying website serves as a repository for all CME programs created.”²⁴⁹
- E. The newsletter, website, and above-described CMEs were all used to spread the false and misleading messages documented in this report.

vii. I have personally experienced this strategy of marketing messages misrepresented as CME. For example, in 2001, every licensed physician in the state of California was mandated to attend a day-long CME course on the treatment of pain as a requirement to maintain licensure. I attended that day-long course, in which use of opioids was promoted. I recall that there was no accurate presentation of the risks of opioids, and the messages that were provided tracked the misconceptions described above regarding overstatement of the benefits of opioids.

g. Clinical Decision Support Tools

- Clinical decision support (“CDS”) tools help doctors know when and how to provide certain types of treatments. In a world of voluminous information, these tools distill complex data into simple-to-read flowcharts and algorithms to guide prescribers. They come in many different forms, from reminders on pocket cards, to infographics on wall posters, to prompts and alerts in the electronic medical record system.²⁵⁰ When based on scientific evidence these tools can be helpful. When not, they can mislead large numbers of doctors.

²⁴⁷ *Id.* at -9664.

²⁴⁸ *Id.*

²⁴⁹ *Id.*

²⁵⁰ U.S. Department of Health and Human Services. *Clinical Decision Support*. (April 10, 2018). <https://www.healthit.gov/topic/safety/clinical-decision-support>.

- ii. For example, in January 2020, Practice Fusion, Inc, a provider of electronic health records (EHRs) including CDS tools embedded within the EHRs, “admitted to conspiring with an opioid manufacturer to create a pain alert tool to encourage physicians to prescribe more extended release opioids,” and agreed to pay \$145 million to resolve criminal and civil allegations that it accepted ‘kickbacks’ in exchange for creating and implementing a CDS that promoted such prescribing.²⁵¹
- iii. According to an article in *JAMA*, “The resulting alerts promoted opioid prescribing that deviated from accepted medical standards by suggesting extended-release opioids as a treatment option for patients with less than severe pain, even if nonopioid or immediate-release opioid alternatives could have adequately controlled the pain. Physicians who received these pain alerts prescribed extended-release opioids at a higher rate than those who did not.”²⁵² A statement by the United States Department of Justice stated, “In marketing the ‘pain’ CDS alert, Practice Fusion touted that it would result in a favorable return on investment for the opioid company based on doctors prescribing more opioids.”²⁵³ Such prescribing exposed patients to increased risks of harms caused by prescription opioids.
- iv. Other examples of clinical decision support tools include items like the “Pain Evaluator” pictured below, described by Endo as a “Pain Assessment tool which will help the HCP [health care provider] understand the patients [sic] pain, not limited to a number on the scale but a clearly [sic] understanding of what they can do because of pain.”²⁵⁴ The Pain Evaluator consists of a series of happy to sad faces, with the happiest face representing “no hurt” and the saddest face representing “hurts worst.” Beyond its grammatical flaws, the Pain Evaluator has never been shown to improve pain outcomes and does not add to understanding patients’ pain. Rather, such tools have been shown to increase opioid prescribing.²⁵⁵

²⁵¹ Taitsman JK, et. al. Commercial Influences on Electronic Health Records and Adverse Effects on Clinical Decision Making. *JAMA Intern Med.* 2020;10.1001/jamainternmed.2020.1318. doi:10.1001/jamainternmed.2020.1318, at p. E1. According to recent reports, Purdue Pharma is the previously unnamed “opioid manufacturer” that conspired with Practice Fusion, and Purdue Pharma has pleaded guilty to that conspiracy. <https://www.nytimes.com/2020/10/21/health/purdue-opioids-criminal-charges.html>

²⁵² *Id.*

²⁵³ US Department of Justice. *Electronic Health Records Vendor to Pay \$145 Million to Resolve Criminal and Civil Investigations* (January 27, 2020). <https://www.justice.gov/opa/pr/electronic-health-records-vendor-pay-145-million-resolve-criminal-and-civil-investigations-0>

²⁵⁴ ENDO-CHI LIT-00023217, at *62 (produced natively).

²⁵⁵ Lembke, “Drug Dealer MD”, fn. 2, above, at p. 66, citing to Vila Jr. H, *et al.* The efficacy and safety of pain management before and after implementation of hospital-wide pain management standards: Is patient safety compromised by treatment based solely on numerical pain ratings? *Anesth Analg.* 2005;101:474-80, and Frasco PE, *et al.* The impact of the Joint Commission for Accreditation of Healthcare Organizations pain initiative on perioperative opiate consumption and recovery room length of stay. *Anesth Analg.* 2005;10:162-8.

Educational Access Tool

Optimize targeting for more efficient deployment of resources on highest potential targets

- **Objective:**
 - To support the sales efforts by providing them with additional educational tools
- **Description:**
 - Pain Assessment tool which will help the HCP understand the patients pain, not limited to a number on the scale but a clearly understanding of what they can do because of pain.
- **Audience:**
 - Call Plan Healthcare Prescribers
- **Timing:**
 - Q1
- **Investment:**
 - \$180,000

How to use the Pain Evaluator
Move the slider from left to right to select your overall pain level.
Next select "yes" or "no" in response to the suggested tasks.
If not applicable, please choose "yes".

What is your overall pain level? *

Are you capable of performing these tasks?

Work: typing, using a mouse, holding a phone, writing, attending meetings, turning pages, lifting weight, sitting at a desk, reading a book

Home: doing laundry, playing with kids, doing dishes, cleaning house, preparing a meal, mowing the lawn, grocery shopping, taking a bath, blow drying hair

Misc.: driving, hiking, riding a bike, sleeping thru night, exercising, walking a dog, walking up stairs, gardening, other recreational activities

Pain Ev. or

How to use the Pain Evaluator

Move the slider from left to right to select your overall pain level.
Next select "yes" or "no" in response to the suggested tasks.
If not applicable, please choose "yes".

What is your overall pain level? *

NO HURT, HURTS LITTLE BIT, HURTS LITTLE MORE, HURTS EVEN MORE, HURTS WHOLE LOT, HURTS WORST

Are you capable of performing these tasks?

Work: typing, using a mouse, holding a phone, writing, attending meetings, turning pages, lifting weight, sitting at a desk, reading a book

Home: doing laundry, playing with kids, doing dishes, cleaning house, preparing a meal, mowing the lawn, grocery shopping, taking a bath, blow drying hair

Misc.: driving, hiking, riding a bike, sleeping thru night, exercising, walking a dog, walking up stairs, gardening, other recreational activities

Pain Evaluator

h. Professional Medical Societies and Patient Advocacy Groups

- i. According to Janssen's response to a May 2012 US Senate Finance Committee request, between 1997-2012 Janssen and its parent, Johnson & Johnson, made payments totaling more than \$4 million dollars to professional societies such as the American Pain Society, the American Academy of Pain Medicine, and the Joint Commission Resources, to promote pain treatment practice guidelines that advocated unwarranted expanded use of opioids.²⁵⁶ From 2012-2017, Janssen continued payments and close coordination with these groups, providing almost a half a million dollars in funding. Janssen also acknowledged making payments via a third party to patient advocacy groups (see below).²⁵⁷

²⁵⁶ JAN-MS-00000001.

²⁵⁷ HSGAC Report, "Fueling an Epidemic", fn. 185, above, at pp. 1, 17.

- ii. The US Senate Finance Committee subsequently issued findings from its investigation into opioid manufacturers' financial relationships with professional medical societies and patient advocacy groups on December 16, 2020.²⁵⁸ According to the Finance Committee's report, "To date, the Committee has identified approximately \$65 million in payments that opioid manufacturers and related companies have made to tax-exempt entities, which suggests that manufacturers view these organizations as helpful extensions of their sales and marketing efforts."²⁵⁹
- The Senate findings show that between 1997 and 2012, the American Pain Society, the American Academy of Pain Medicine, and the American Pain Foundation, among others, received significant funding from Endo (\$13.5 million), Johnson & Johnson (\$4.0 million), and Purdue (\$18.7 million).²⁶⁰ The American Pain Society, for example, received more than \$3.3 million in funding from 2012 through 2017 from more than a dozen opioid manufacturers, including Endo, Janssen, Mallinckrodt, Purdue and Teva.²⁶¹ In 2012, a separate Senate committee report stated that these manufacturer-supported professional medical societies and patient advocacy groups "have amplified or issued messages that reinforce industry efforts to promote opioid prescription and use, including guidelines and policies minimizing the risk of addiction and promoting opioids for chronic pain."²⁶²
- iv. While the Senate Finance Committee investigation is on-going, the "initial review has revealed troubling instances in which patient advocacy groups, and other tax-exempt organizations, their officers, and their board members have engaged in initiatives that appear to echo and amplify messages to increase use of opioid manufacturers' drugs, including abuse-deterrent opioids that have not been proven to be any less addictive than other types opioids.[sic]"²⁶³
- v. Joel Saper, M.D., a past board member of the American Pain Society (APS), testified that the American Pain Society (APS) received financial support from the Pharmaceutical Opioid Industry, which he referred to as "narcopharma."²⁶⁴

²⁵⁸United States Senate Committee on Finance, Findings from the Investigation of Opioid Manufacturers' Financial Relationships with Patient Advocacy Groups and other Tax-Exempt Entities (December 16, 2020)

<https://www.finance.senate.gov/imo/media/doc/2020-12-16%20Finance%20Committee%20Bipartisan%20Opioids%20Report.pdf>.

²⁵⁹ *Id.*, at p. 2.

²⁶⁰ *Id.*, at Appendix A.

²⁶¹ *Id.*, at Appendix B.

²⁶² HSGAC Report, "Fueling an Epidemic", fn. 185, above, at p. 12.

²⁶³ Senate Finance Committee, "Findings", fn. 258, above, at p. 17.

²⁶⁴ Saper, "The Influence of Pharma," fn. 167, above, at p. 5.

- vi. Consistent with and supportive of my personal experience, Dr. Saper testified that “the educational programs of AAPM [American Academy of Pain Management] and APS particularly as they involve opioid advocacy, were greatly influenced by commercial largess. In my opinion, commercial dynamics influenced, if not steered, the selection of abstracts, course topics, and faculty to commercially friendly participants as it involved opioid advocacy, largely ignoring those imposing or exhorting caution against the growing advocacy for opioids for chronic nonmalignant pain.”²⁶⁵
- vii. Dr. Saper testified that such educational programs of AAPM and APS involving opioid advocacy were “inappropriate”,²⁶⁶ and I agree.
- viii. Dr. Saper further stated that “APS and AAPM and its members have participated, if not promoted, this crisis by failing to assure the presentation of unbiased, balanced educational programs and guideline development, thereby protecting the public from commercial influence through undisclosed support from the opioid industry. In failing to do so, the organizations failed to protect patients.”²⁶⁷
- ix. In 2009, Janssen partnered with the American Geriatrics Society and American Academy of Pain Medicine to create a 2009 patient education guide entitled, “Finding Relief: Pain Management for Older Adults.”²⁶⁸ In 2010, Janssen paid the American Geriatrics Society more than \$158,209 for “educational grants.”²⁶⁹
- x. The “Finding Relief” patients’ guide included the claims shown below.²⁷⁰ These claims were false and misleading in that addiction to prescription opioids is common, not rare, and chronic use does not confer substantial benefit, as discussed later in this Report.

²⁶⁵ Deposition of Joel R. Saper, M.D., January 11, 2019, MDL No. 2804, at 92:13-22.

²⁶⁶ *Id.*, at 93:15-19.

²⁶⁷ *Id.* at 115:24-116:6.

²⁶⁸ HSGAC Report, “Fueling an Epidemic”, fn.185, above, at p. 13.

²⁶⁹ JAN-MS-00000001 at 0007.

²⁷⁰ JAN-MS-00000306 at 0315.; *see also* JAN00000306.

Opioid myths

Myth: Opioid medications are always addictive.

Fact: Many studies show that opioids are *rarely* addictive when used properly for the management of chronic pain.

Myth: Opioids make it harder to function normally.

Fact: When used correctly for appropriate conditions, opioids may make it *easier* for people to live normally.

Myth: Opioid doses have to get bigger over time because the body gets used to them.

Fact: Unless the underlying cause of your pain gets worse (such as with cancer or arthritis), you will probably remain on the same dose or need only small increases over time.

- xi. Further, an internal Purdue Pharma email from Richard Sackler to Paul Goldenheim, dated April 13, 2001, concerned a planned meeting with “leaders of APS, APF [American Pain Foundation] and other pain societies.” Dr. Sackler stated, “Our goal is to bind these organizations more closely to us than heretofore, but also to align them with our expanded mission and to see that the fate of our product(s) are [sic] inextricably bound up with the trajectory of the pain movement.”²⁷¹
- xii. The Pharmaceutical Opioid Industry targeted more than just physician-membership professional medical societies. For example, nursing societies were also prominently featured as part of their marketing campaign. The Endo “2009 OPANA Brand Strategic Plan” indicates that it would increase “OPANA ER brand awareness at venues where Specialty HCP [health care providers] attend” including the “American Academy of Pain Medicine, American Conference on Pain Medicine, Oncology Nurses Society, American Pain Society, American Society for Pain management [sic] Nursing, American Society of Anesthesiologist [sic], American College of Rheumatology.”²⁷² As noted in my article referenced at Section §C.4.k, above, nurse practitioners are among the highest opioid

²⁷¹ PPLPC045000004928 at 4929

²⁷² ENDO-CHI_LIT-00023217, at *51 (produced natively)

prescribing health care professionals, thus targetting such professionals would be expected to increase sales.

- i. The Federation of State Medical Boards
 - i. The Federation of State Medical Boards (FSMB) is a national organization that oversees the 70 medical and osteopathic boards of the United States and its territories. The State Board organizations serve many functions, but the most important is to exert disciplinary action against doctors who are deemed dangerous to patients. One of the most severe forms of disciplinary action is to revoke a doctor's license to practice medicine.
 - ii. In 1998, the FSMB released a policy to reassure doctors that they would not be prosecuted if they prescribed even large amounts of opioids, as long as it was for the treatment of pain. Further, the FSMB urged state medical boards to punish doctors for under-treating pain. Doctors lived in fear of disciplinary action from the State Medical Boards and the lawsuit that usually followed, if they denied a patient opioid painkillers.
 - iii. Between 2007 and 2012, the FSMB received approximately \$1.3 million in funding from Purdue, Johnson & Johnson and Endo.²⁷³
 - iv. In 2007, the FSMB published a book promoting the use of opioid painkillers. This book was sponsored by a "consortium" that included Abbott Laboratories, Alpharma Pharmaceuticals, Cephalon, Inc., Endo Pharmaceuticals, and the University of Wisconsin Pain and Policy Study Group ("PPSG").²⁷⁴ (*See* Appendix II.)
 - v. As detailed in Appendix II to this Report, the Pharmaceutical Opioid Industry provided substantial funding to the PPSG, which lobbied State Medical Boards to increase access to opioids, preclude punishment if opioids were prescribed for pain, and classify undertreatment of pain as inappropriate conduct. PPSG played a central role in revising the Federation of State Medical Board's Model Guidelines on the Use of

²⁷³ Senate Finance Committee, "Findings", fn. 258, above, at pp. 9-10. The Findings note that the FSMB "appears to have changed its policy shortly after the [Senate Finance] Committee's 2012 inquiry" and no longer accepts grants or funding from pharmaceutical companies.

²⁷⁴ Fishman, S.(ed.), "Responsible Opioid Prescribing: A Physician's Guide" (Federation of State Medical Boards, Waterford Life Sciences, 2007). The 2020 US Senate Finance Committee findings note that these types of "industry-developed materials and talking points frequently downplayed or distracted from the addictive nature of prescription opioids" and "these efforts directly influenced the medical community, causing them to widely believe that there was a low risk for addiction among patients with chronic pain – a false narrative promoted by opioid manufacturers to increase use of their opioid products", fn. 258, above, at p. 8.

Controlled Substances for Pain Management,²⁷⁵ now entitled Model Policy for the Use of Controlled Substances for Pain Management.²⁷⁶

- vi. The American Pain Society, funded and influenced by the Pharmaceutical Opioid Industry, supported PPSG professors David Joranson and June Dahl to “visit boards of medicine in state after to state to argue the importance of lessening the regulation of doctors who prescribe opioids for cancer, acute, and end-of-life pain.”²⁷⁷
- vii. Drs. Joranson and Dahl, as part of their state to state campaign, designated each state with a letter grade based on their evaluation of state policies that “enhance” or “impede” opioid prescribing.²⁷⁸ The PPSG had created a hierarchy of letter grades to assess the ‘improvement’ or lack of improvement in making opioids easier to prescribe with fewer penalties to prescribing physicians.²⁷⁹ The highest grade, from the PPSG’s standpoint, was an “A.” A grade of “C” meant that PPSG considered a particular state to have policies that “impede pain management” and opioid prescribing.
- viii. The Pharmaceutical Opioid Industry and PPSG influenced states to adopt pain laws that encouraged opioid prescribing by shielding physicians from liability, and by making it difficult to refuse to prescribe opioids to patients who request them. As stated in a 2013 report from the Ohio House of Representatives, “The General Assembly passed the Intractable Pain Act in 1998, opening the floodgates for doctors to treat chronic pain with prescription opioids. While the driving force was to treat terminal cancer patients, the legislation effectively allowed physicians to prescribe opioid for pain in any number of situations. Up until the late 1990s, opioid were used only sparingly.”²⁸⁰ According to PPSG’s ranking system, Ohio received a Grade of “B” in 2000-2010, and “improved” to a “B+” in 2012.²⁸¹ According to PPSG, Ohio “improved” its grade by repealing the term “intractable pain” from state statutes,²⁸² replacing the term ‘intractable pain’ with “chronic pain.”²⁸³ According to a PPSG evaluation

²⁷⁵ WIS_PPSG_008292.

²⁷⁶ Federation of State Medical Board’s Model Guidelines on the Use of Controlled Substances for Pain Management (2004), http://web.archive.org/web/20050612075051/http://www.fsmb.org/Policy%20Documents%20and%20White%20Papers/2004_model_pain_policy.asp

²⁷⁷ Saper, “The Influence of Pharma,” fn. 167, above, at p. 9.

²⁷⁸ PPLPC036000002758, at -2778

²⁷⁹ PPLPC017000046138, at -6154

²⁸⁰ Ohio House “Chairman’s Report”, fn. 71, above, at p. 6.

²⁸¹ PPLPC017000046138 at -6151; *See also*, PPLPC017000514276, at -4282.

²⁸² Pain and Policy Studies Group. Achieving Balance In State Pain Policy: a progress report card (CY 2012). 2013:1-40, at p. 19. <http://www.painpolicy.wisc.edu/sites/www.painpolicy.wisc.edu/files/evalguide2012.pdf> (last accessed December 18, 2020)

²⁸³ Ohio Revised code § 4731.052 (effective 9/10/2012).

guide this change meant the law now governed the treatment of all types of pain.²⁸⁴ This change was contrary to good medical practice, and to what has been recommended in revised guidelines today. Ohio's intractable pain law has since been revised to include a more involved series of steps that a prescribing doctor must take regarding discussion of the risks, monitoring for misuse and diversion, referring to pain and addiction medicine specialists, prescribing naloxone, and discontinuing opioids when harms outweigh benefits.²⁸⁵ Such belated restrictions have been, however, insufficient to unwind the damage done by prior enactment of legislation that encouraged the increased prescribing of opioids.

- ix. In addition to the indirect support by the Industry through the APS, direct financial support to PPSG was provided by the Pharmaceutical Opioid Industry, as revealed in documents produced by PPSG and summarized in Appendix II to this Report. Those documents show substantial contributions by several opioid manufacturers, including Janssen, Endo, Ortho-McNeil (an affiliate of Johnson and Johnson), Alpharma,²⁸⁶ and Cephalon, over a period of over a decade, during which PPSG justified its recurring requests for further funding on the basis of its successful efforts to loosen restrictions on opioid prescribing by lobbying State Medical Boards, presentations at professional conferences, leading industry-friendly Continuing Medical Education seminars, and publications in the scientific literature. (See Appendix II to this Report).
- x. J&J and Janssen worked with the Robert Wood Johnson Foundation ("RWJF"), which paid \$5,926,294.00 in grants to the University of Wisconsin-Madison School of Medicine, the eventual home of the PPSG between 1997 and 2004.²⁸⁷ Dr. Richard Payne, co-chair of the National Pain Education Council (NPEC) with Russell Portenoy, was on the Janssen and RWJF medical advisory boards during overlapping periods.²⁸⁸ NPEC was a Janssen-funded patient advocacy group which Janssen

²⁸⁴ WIS_PPSG_018284 at p.20.

²⁸⁵ Ohio Admin. Code §4731-11-14; *See, e.g.*, Pinke, E.J. Standards for Use of Opiates in Treatment of Pain Changes in Ohio, *The National Law Review*. 2018:7;361. <https://www.natlawreview.com/article/standards-use-opiates-treatment-pain-changes-ohio>

²⁸⁶ Actavis (now Allergan) acquired Kadian from Alpharma in 2008; *see* Press Release, Actavis, Actavis Acquires Kadian; Extends Specialty Drug Portfolio in U.S., (Dec. 30, 2008), <https://www.businesswire.com/news/home/20081230005227/en/Actavis-Acquires-Kadian-Extends-Specialty-Drug-Portfolio>.

²⁸⁷ MDL_RWJF_0000001: Grant ID 032037 for \$1,601,991; MDL_RWJF_0000003: Grant ID 036509 for \$998,000; MDL_RWJF_0000004: Grant ID 036547 for \$998,865; MDL_RWJF_0000005: Grant ID 037589 for \$1,408,628; MDL_RWJF_0000009: Grant ID 043412 for \$200,450; MDL_RWJF_0000010: Grant ID 043940 for \$421,800; MDL_RWJF_0000012: Grant ID 048204 for \$183,680; MDL_RWJF_0000013: Grant ID 051813 for \$112,880.

²⁸⁸ JAN-MS-00402671.

launched in support of the Duragesic tactical plan.²⁸⁹ RWJF also funded the creation and dissemination of the Model State Guidelines through the Federation of State Medical Boards and its collaboration with PPSG, and provided funding to The Joint Commission as well.²⁹⁰

- xi. Despite the absence of reliable evidence for the use of long-term opioid therapy in the treatment of chronic pain, the Pharmaceutical Opioid Industry sought to shame prescribers into opioid prescribing by claiming that the ‘failure’ to prescribe opioids was tantamount to causing pain, and to scare them into prescribing by suggesting reprisal from regulatory bodies like the FSMB. In their promotional material and “Train the Trainer” course, Defendants frequently invoked sources that characterized opioid prescribing as a moral obligation, and the failure to prescribe as the equivalent of causing pain, leading to legal sanctions. (See Appendix I for more detail)
- xii. I remember how the fear of “undertreating pain” permeated medical practice and culture at this time. Doctors in some states were subject to the risks of disciplinary action from the board and lawsuits that could follow if they denied a patient’s request for opioids.

j. The Joint Commission

- i. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO), often simply referred to as “The Joint Commission” (TJC), is a United States-based nonprofit tax-exempt 501(c) organization that accredits health care organizations and programs in the United States. The Joint Commission arose out of a movement in the 1950s to reform hospitals by looking at whether or not patients got better. JCAHO went through a consolidation of power over the years, combining multiple medical organizations under one roof, simplifying its name in 2007 to “The Joint Commission.” Its positioning statement is “Helping Health Care Organizations Help Patients.”²⁹¹
- ii. In response to an inquiry from the U.S. Senate Finance Committee, a 2012 letter from The Joint Commission stated that The Joint Commission had received funding from Purdue over a 4-year period from 1999-2002, “for several activities, primarily involving knowledge transfer related to The Joint Commission’s pain management standards, although Purdue also funded an effort on metrics development. Purdue’s support facilitated the efficient, effective and widespread dissemination of the new pain management standards that were developed by The Joint Commission

²⁸⁹ JAN-MS-00306713.

²⁹⁰ PDD1706042217.

²⁹¹ The Joint Commission, <http://www.jointcommission.org/>.

with modest support from the University of Wisconsin (and no support from Purdue).”²⁹² The 2012 Joint Commission letter also states that support for its “pain management activities” was provided by Purdue, Endo Pharmaceuticals, Ortho-McNeill, The National Pharmaceutical Council, Pfizer, and Abbott Labs.²⁹³ An attachment to the 2012 letter disclosed a total of \$3,911,942 in “payments or transfers received [by the Joint Commission] from all organizations that develop, manufacture, produce, market, or promote the use of opioid-based drugs.”²⁹⁴

- According to the US Senate Finance Committee Findings of December 16, 2020, The Joint Commission received over \$2.7 million in funding from Defendants Endo, Johnson & Johnson, and Purdue between 2000-2012.²⁹⁵
- Today, having Joint Commission accreditation is required for many hospitals and clinics to remain licensed. Payment for services from the Centers for Medicare and Medicaid Services (CMS), the largest federally funded insurance program, is also contingent on TJC approval. TJC approval is obtained through periodic surveys.
- v. In 2001, The Joint Commission made pain the fifth vital sign, alongside heart rate, temperature, respiratory rate, and blood pressure, and promoted the use of the Visual Analog Scale (VAS), a series of happy or sad faces supposedly corresponding to pain levels from 0 (no pain) to 10 (the most extreme pain),²⁹⁶ exemplified by Endo’s Pain Evaluator. The Joint Commission sold educational materials to hospitals so they could meet the standards of pain treatment that would be required to pass the next Joint Commission Survey. These materials included laminated cards and posters of the Visual Analog Scale of pain, as well as teaching videos promoting more liberal prescribing of opioids for pain, including misleading statements such as: “Some clinicians have inaccurate and exaggerated concerns about addiction, tolerance and risk of death.... This attitude prevails despite the fact there is no evidence that addiction is a significant issue when persons are given opioids for pain control.”²⁹⁷ Per the GAO 2003 report, “During 2001 and 2002, Purdue funded a series of nine programs throughout the country to educate hospital physicians and staff

²⁹² Letter from The Joint Commission to Senators Baucus and Grassley, June 29, 2012, at p. 3.

https://www.finance.senate.gov/imo/media/doc/35.%20Joint%20Commission%20Letter%20to%20Sens%20Baucus%20and%20Grassley%20_June.29.2012.pdf. The 2012 Joint Commission letter does not state that the University of Wisconsin itself was funded by Purdue, through the grants to its Pain and Policy Study Group.

²⁹³ *Id.*

²⁹⁴ *Id.*, at p. 2 and Attachment A at TJC_000000001.

²⁹⁵ Senate Finance Committee, “Findings”, fn. 258, above, at Appendix A. The Senate Findings show that from 2000 through 2012, The Joint Commission received \$75,000 in funding from Endo, \$515,244 from Johnson & Johnson and more than \$2 million from Purdue Pharma.

²⁹⁶ Lembke, “Drug Dealer MD”, fn. 2, above, at p. 66.

²⁹⁷ Catan T, Perez E., “A Pain Drug Champion Has Second Thoughts”. *The Wall Street Journal*. December 2012, at p.4.

on how to comply with JCAHO's pain standards for hospitals and to discuss postoperative pain treatment. Purdue was one of only two drug companies that provided funding for JCAHO's pain management educational programs. Under an agreement with JCAHO, Purdue was the only drug company allowed to distribute certain educational videos and a book about pain management; these materials were also available for purchase from JCAHO's Web site. Purdue's participation in these activities with JCAHO may have facilitated its access to hospitals to promote OxyContin."²⁹⁸

- vi. On December 31, 2000, an internal Purdue email from Robin Hogen to Mortimer Sackler, MD, responded to Dr. Sackler's assertion that more articles were needed "to help counteract the negative articles in the national media." Hogen's email, regarding press coverage of JCAHO pain guidelines, stated, "With respect to generating more articles about pain guidelines, we 'loaned' JCAHO our PR firm (Fleishman Hillard) last year during the national roll out of the new standards. I suspect some of these stories which are now breaking at year-end were generated by media contacts made several months ago. We could certainly renew that grant (\$75k) this year- to generate as much positive, unbranded publicity about the new pain standards and the chronic undertreatment of pain in America. Good idea." This exchange supports my opinion that the Pharmaceutical Opioid Industry played a significant, insidious role in the epidemic of over-prescribing of opioids, by funding the widespread promotion of standards that mandated pain treatment, while the medical profession and the public were unaware of Industry's hidden role.²⁹⁹
- vii. As noted above, J&J and Janssen worked with the RWJF to support the Wisconsin PPSG. These entities also worked together to provide funding to The Joint Commission (JCAHO).
- viii. As in the case of Defendant-supported KOL's, professional medical societies, and patient advocacy groups, the JCAHO and PPSG (financially supported by Janssen and RWJF) were instrumental in creating new pain treatment standards that promoted increased opioid use as well as opioid-friendly prescribing guidelines in the early 2000s.
- k. Examples of Misrepresentations: "Pseudoaddiction" and "Breakthrough Pain"
 - The Pharmaceutical Opioid Industry created promotional material misrepresented as educational material; and disseminated this mis-education through all the modalities described above. Misleading concepts

²⁹⁸GAO. Prescription OxyContin Abuse and Diversion and Efforts to Address the Problem. *J Pain Palliat Care Pharmacother*. 2003;18(3):109-113. doi:10.1300/J354v18n03_12, at p.23.

²⁹⁹ PDD8801183361 at 3363.

such as “pseudoaddiction” and “breakthrough pain” provide two prominent examples.

- ii. Defendants mischaracterized addictive behavior as “pseudoaddiction.”
 - A. Based on a single case report of a patient who engaged in drug-seeking behavior,³⁰⁰ doctors were encouraged to conceptualize the patient’s addictive behavior as evidence of under-treated pain. This case report was co-authored by David Haddox. The authors of the case report incorrectly asserted that treatment of pain is often inadequate because of “excessive fears of tolerance and dependence by both health professionals and the public,”³⁰¹ when in fact those fears are well-justified and should be respected. In addition, since the conditions of addiction and dependence are common, their recommended treatment to continue administering or even increase opioids despite addictive behavior, undoubtedly puts more patients at risk of becoming addicted or dependent.
 - B. There is no such thing as “pseudoaddiction,” and no evidence that providing more opioids is an appropriate response to patients exhibiting drug-seeking behavior. On the contrary, tolerance, dependence, and withdrawal, markers of neuroadaptation to the drug, constitute an adverse medical reaction and should trigger consideration of tapering the opioid medication, not increasing its dose.
 - C. In a review article on use of the term “pseudoaddiction,” the authors found, “By 2014, pseudoaddiction was discussed in 224 articles. Only 18 of these articles contributed to or questioned pseudoaddiction from an anecdotal or theoretical standpoint, and none empirically tested or confirmed its existence. Twelve of these articles, including all four that acknowledged pharmaceutical funding, were proponents of pseudoaddiction. In contrast, six articles, none with pharmaceutical support, questioned pseudoaddiction as a clinical construct.”³⁰² Further, the authors wrote, “In conclusion, we find no empirical evidence yet exists to justify a clinical ‘diagnosis’ of pseudoaddiction.”³⁰³ I agree that there is no empirical evidence to justify a diagnosis

³⁰⁰ Weissman DE, Haddox JD. Opioid pseudoaddiction--an iatrogenic syndrome. *Pain*. 1989; 36(3):363-366. <http://www.ncbi.nlm.nih.gov/pubmed/2710565>.

³⁰¹ *Id.* at p. 365.

³⁰² Greene MS, Chambers RA. Pseudoaddiction : Fact or Fiction? An Investigation of the Medical Literature. *Curr Addict Rep* 2015:310-317. doi:10.1007/s40429-015-0074-7, at p. 310.

³⁰³ *Id.* at p. 314.

of pseudoaddiction, and that use of this term was spread by the manufacturers of prescription opioids, with the explicit and dangerous message to doctors that more opioids should be prescribed.

- D. To “correctly define addiction” the Pain and Policy Study Group (PPSG), discussed above, took consensus definitions from the Pharmaceutical-Opioid-Industry-funded American Society of Addiction Medicine, American Academy of Pain Medicine, and the American Pain Society.³⁰⁴ Those included a definition of the term pseudoaddiction: “Pseudoaddiction is a term which has been used to describe patient behaviors that may occur when pain is undertreated. Patients with unrelieved pain may become focused on obtaining medications, may ‘clock watch,’ and may otherwise seem inappropriately ‘drug seeking.’ Even such behaviors as illicit drug use and deception can occur in the patient’s efforts to obtain relief. Pseudoaddiction can be distinguished from true addiction in that the behaviors resolve when pain is effectively treated.”³⁰⁵ Thus, PPSG, an entity funded by the Pharmaceutical Opioid Industry, aligned with and promoted the Industry-supported view of “pseudoaddiction” as a real diagnosis for which more opioids were the prescribed treatment. (See Appendix II to this report). Dr. Portenoy later criticized the Pharmaceutical Opioid Industry’s use of the term pseudoaddiction.³⁰⁶
- E. The 1998 Industry-influenced guidelines of the Federation of State Medical Boards, discussed above, incorporate the concept of pseudoaddiction,³⁰⁷ providing further evidence of industry’s influence over the FSMB.

iii. Defendants mischaracterized tolerance as “breakthrough pain”

- A. “Breakthrough pain” is a term used by the Pharmaceutical Opioid Industry to describe a heightened state of intermittent pain that exceeds the analgesic capacity of the patients’ underlying chronic opioid dose. In fact, “breakthrough pain” is far more likely to represent the patients’ declining response to their prescribed opioids due to the well-established effect of

³⁰⁴ WIS_PPSG_002042, June 8, 2001.

³⁰⁵ *Id.*

³⁰⁶ Declaration of Russell K. Portenoy, M.D. in MDL 2804, at ¶ 44.

³⁰⁷ Federation of State Medical Boards. *Model Guidelines for the Use of Controlled Substances for the Treatment of Pain* (May 2, 1998), https://painpolicy.iu.edu/sites/default/files/sites/www.painpolicy.wisc.edu/files/model_0.pdf.

tolerance, whereby a greater opioid dose is needed to attain the same effect over time. The addition of ACTIQ or other opioids for so-called “breakthrough pain” represents an increased opioid dose that adds to patients’ risk of adverse effects.

- B. Tolerance is the need for more and more of the drug to get the same effect. As the opioid dose is increased to overcome tolerance to the pain-relieving effects of the drug, patients are exposed to the other dose-dependent risks associated with opioids, including the risk of death. Furthermore, tolerance to the respiratory suppressant effects (the ability of opioids to decrease breathing rate and thus blood oxygenation) develops more slowly than tolerance to the pain-relieving effects of the drug. As such, as the dose of opioids goes up to target pain relief, the breathing rate goes down, increasing the risk of accidental overdose and death.³⁰⁸ Tolerance is not a short-lived phenomenon. It persists and renders the opioid largely ineffective for the underlying pain condition. Despite tolerance, patients often endorse ongoing subjective benefit from the opioid, not because it is treating underlying pain, but because it is relieving the pain of opioid withdrawal from the previous dose.
 - C. Once tolerance occurs, patients may experience opioid withdrawal multiple times a day between pain pill doses and need higher and higher doses to avoid between-pill withdrawal. Tolerance, dependence, and withdrawal, markers of neuroadaptation to the drug, constitute an adverse medical reaction and should trigger consideration of tapering the opioid medication. Instead, in the 1990s and early 2000s, Defendants’ promotional messages advised doctors that tolerance should be addressed by adding short-acting opioids to long-acting opioids for “breakthrough pain,” or by “rotating” to another opioid.
 - D. As explained more fully in Appendix I.B. to this Report, Defendants marketed opioids such as ACTIQ as “the ideal agent” for breakthrough chronic pain.³⁰⁹ This promotional message was misleading and contributed to opioid over-exposure.
1. These documents and testimony support my opinion that the Pharmaceutical Opioid Industry improperly supported the pro-opioid mis-education of medical professionals and patients in order to increase sales of prescription opioids that

³⁰⁸ Lembke, *et al.*, “Weighing the Risks,” fn.4, above, at p. 987; Chou R, Deyo R, Devine B, *et al.* The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain. *Evid Rep Technol Assess* (Full Rep). 2014;218(218):63. doi:10.23970/AHRQEPERTA218, at p. ES-25.

³⁰⁹ TEVA_CAOC_00759630 at 9633.

resulted in an unprecedented epidemic of drug-induced mortality and morbidity. As I have written and stated elsewhere, others bear some responsibility for the over-prescribing of opioids for chronic pain. However, the Pharmaceutical Opioid Industry bears the far greater share of the responsibility for its role in promoting false messages of substantial benefit and low risk of opioids, and in providing the excessive supply that fueled the epidemic.

- m. My opinions stated above are consistent with, and supported by, the ASPPH Report referenced above, which found, “The medical community became more aggressive in its use of opioids in response to a multi-faceted pharmaceutical industry-funded campaign that downplayed opioid risks and exaggerated benefits,” and that “the opioid crisis was caused largely by deceptive marketing.”³¹⁰ The ASPPH Report also stated, “The opioid crisis can be directly tied to practices adopted and encouraged by opioid manufacturers and distributors. As such, the industry’s credibility is near zero”³¹¹

5. Opioid distributors collaborated with opioid manufacturers and pharmacies to promote sales of opioid pain pills. Such coordinated efforts included programs to give away free samples of opioids, coupons to discount opioids, and promotion of specific opioid products under the guise of education. These activities increased the population of opioid users, dose and duration of opioid use, and the risk of opioid misuse, addiction, dependence, and death.

- a. Opioid distributors worked in close collaboration with opioid manufacturers and pharmacies to promote sales of opioid pain pills. The claim that distributors were indifferent transporters of opioid pain pills between manufacturers and pharmacies (‘We’re just the trucks’) is refuted by the many documents demonstrating a coordinated partnership to promote prescription opioid consumption, as well as a quid pro quo reimbursement structure. At every step in the supply chain, money flowed. There was a coordinated, psychologically sophisticated effort which appeared on its face to be about helping patients save money, ‘overcome barriers,’ and ‘adhere to medical treatment,’ but was in fact an elaborate scheme designed to promote sales of specific opioid products.
- b. Distributors, manufacturers, and pharmacies collaborated to offer free and discounted samples of dangerous and addictive opioids. As any drug dealer can tell you,³¹² free samples are a tried and true way to hook consumers and secure future sales. Further, once patients become dependent on opioids, their continued consumption is income and price sensitive, making them vulnerable to discounted products.

³¹⁰ ASPPH Report, “Bringing Science”, fn. 16, above, at p. 7; emphasis added.

³¹¹ *Id.* at 32.

³¹² “Drug Dealer Admits to Giving Free Sample.” https://www.herald-dispatch.com/news/drug-dealer-admits-to-giving-free-sample/article_ce289f74-e9c3-58ce-8cce-d7483e774627.html; dealer “admitted he provided the free sample of drugs to secure future sales...”

- i. “When a reduction in income is anticipated, it is predicted that consumption will decrease. When subsidies are eliminated, the reaction is similar to a decrease in income.”³¹³ By offering free samples for prescription opioids, the Opioid Pharmaceutical Industry created customers in the form of opioid-dependent patients, and then kept them coming back with discounted prices. I observed these economic factors exert their influence among my own patients. Prescription opioids and illicit heroin/fentanyl are interchangeable in terms of their addictive and euphoric effects, and my patients would commonly use whichever opioid was more readily available at the lowest price.
- ii. McKesson collaborated with Janssen to give away free fentanyl, an opioid that is 50 times more potent than heroin. Branded advertisements promoted the free-give-away of 5 x 25 mcg Duragesic fentanyl patches, claimed by submitting a voucher to McKesson.³¹⁴
- iii. McKesson directly targeted patients as well as pharmacists. McKesson described its “US-based, healthcare-dedicated contact center”³¹⁵ which delivers “patient-centric behavioral coaching”³¹⁶ as part of its broader “Behavioral Call Campaign” wherein “Agents make outbound calls to patients in order to uncover personal barrier and provide appropriate messaging/content to help overcome those barriers.”³¹⁷ These efforts, claim McKesson, are “aligned to address Janssen’s needs.”³¹⁸
- iv. McKesson partnered with Janssen to give away free and discounted Nucynta and Nucynta ER. A “Nucynta ER/Nucynta New 10 Free Pills Program” from September 1, 2011 to December 31, 2012, gave patients free drug.³¹⁹ Per this document, where the “10 Free Pills” program was in place, “Average monthly claims [went] up 198% over 2011.”³²⁰ When an older “10 Free Pills” program was phased out, Nucynta claims went down.³²¹
- v. McKesson’s Nucynta promotional programs also included a Pay No More Than \$25 voucher card and a \$20 off savings card.³²² As of the end of November 2010 there were 56,641 claims for the voucher card and 66,885

³¹³ Roddy J, Steinmiller CL, Greenwald MK. Heroin purchasing is income and price sensitive. *Psychol Addict Behav.* 2011;25(2):1-14, at p.5

³¹⁴ MCKMDL00334317. On the back end, Janssen trained its sales reps to promote the free fentanyl patches to doctors, as discussed above, at Section §C.4.c.xxv.

³¹⁵ JAN-MS-01071368 at -1428.

³¹⁶ *Id.* at -1427.

³¹⁷ *Id.* at -1426.

³¹⁸ *Id.* at -1424.

³¹⁹ *Id.*, at -1399.

³²⁰ *Id.*, at -1401.

³²¹ *Id.*, at -1408.

³²² JAN-MS-01130535

claims for the savings card.³²³ Furthermore, for the voucher card, Ohio was sixth in nation in claims, resulting in \$85,747 in savings.³²⁴ McKesson's pharmacy analysis for the voucher card identified Walgreens, CVS, Wal-Mart and Rite Aid in as the top four pharmacies in claims processed with Walgreens and CVS accounting for 47.2%.³²⁵

- vi. McKesson collaborated with both manufacturers and pharmacies through its LoyaltyScript and TrialScript programs. The programs utilized trial offers, savings cards, and e-coupons to promote opioids including OxyContin, Butrans, Hysingla, Ultram ER, Magnacet and Nucynta.³²⁶ Patients would redeem the manufacturer's offer at the pharmacy and then the pharmacy would submit claims for reimbursement to McKesson.³²⁷ The LoyaltyScript program for Magnacet paid a \$50 benefit, and by August 2008 there were 6,946 total paid Magnacet claims.³²⁸ The State of Ohio accounted for 7.2% of these claims, placing it at third most in claims per state.³²⁹ Additionally, McKesson's own pharmacy analysis ranked Walgreens, CVS, Rite Aid, and Walmart all in the top six of claims processed, with Walmart and CVS together accounting for 49% of all claims.³³⁰ McKesson also collaborated with Janssen on a Nucynta TrialScript Program that utilized voucher cards.³³¹ By the end of November 2010 there were 17,509 Nucynta TrialScript claims, with Ohio accounting for 5.6%, the fourth highest state in the nation.³³² McKesson's pharmacy analysis ranked Walgreens, CVS, Walmart, and Rite Aid as the top four pharmacies in claims processed, with Walgreens and CVS accounting for 43% of claims.³³³

- A. In 2011, McKesson reminded Johnson & Johnson that "just as the McKesson/J&J partnership dates back as far as 1939, the relationship between J&J and MPRS [McKesson Patient Relationship Solutions] dates back to the 1990s when we first implemented acquisition and adherence programs. Since then,

³²³ *Id.*, at -0545, -0554.

³²⁴ *Id.*, at -0546.

³²⁵ *Id.*, at -0547.

³²⁶ MNK-T1_0006717600; JAN-MS-01130535; MCKMDL00385864. Magnacet was a Mallinckrodt product, initially marketed in June 2007, that combined various doses of the opioid oxycodone with 400 mg of acetaminophen, *see* [https://www.biospace.com/article/releases/-b-mallinckrodt-b-launches-magnacet-tm-tablets-/#:~:text=The%20U.S.%20Food%20and%20Drug,moderate%20to%20moderately%20severe%20pain](https://www.biospace.com/article/releases/-b-mallinckrodt-b-launches-magnacet-tm-tablets-/#:~:text=The%20U.S.%20Food%20and%20Drug,moderate%20to%20moderately%20severe%20pain.). Operating through "MaxCare," a Pharmacy Benefit Manager, Mallinckrodt offered a "Patient Assistance Program" that provided all doses of Magnacet, among other products, for a \$20 co-pay. *See* https://www.rxhope.com/pap/pdf/mallinckrodt_pharma_0209.pdf.

³²⁷ MCKMDL00385864 at p. 2.

³²⁸ MNK-T1_0006717600 at *4, *7 (produced natively).

³²⁹ *Id.*, at *12.

³³⁰ *Id.*, at *14.

³³¹ JAN-MS-01130535

³³² *Id.*, at -0539-0540.

³³³ *Id.*, at -0541

our relationship has matured and flourished as we have had the pleasure of managing numerous J&J retention programs” including Nucynta IR TrialScript, Nucynta IR LoyaltyScript Pay No More Than \$25, Nucynta IR LoyaltyScript \$20 Savings Card.³³⁴ McKesson went on to boast that their LoyaltyScript programs “*delivered an average of 2.4 times more prescriptions over 12 months than a control group of similar patients prescribed the same drug but were not in the program, in a recent study. The two Nucynta IR LoyaltyScript programs (Pay no more than \$25 and \$20 Savings Card) combined have produced close to 150,000 claims to date.*”³³⁵

- vii. McKesson partnered with Purdue to distribute a “Butrans Savings Card.”³³⁶
- viii. Cardinal Health partnered with Actavis to promote Kadian co-pay assistance cards with up to \$50 savings on Kadian prescriptions, with “no expiration” date cards available in 2011.³³⁷ Actavis expanded the Kadian coupon program in October 2011 with co-pay coverage up to \$1,200 per year.³³⁸ The explicit goals of the program were to “Facilitate new therapy starts”³³⁹ and “Increase the average length of therapy.”³⁴⁰
- c. Opioid distributors collaborated with opioid manufacturers to advertise specific opioid products.
 - i. AmerisourceBergen collaborated with Janssen to advertise Nucynta for a fee of \$10,000 for a 2 week marketing campaign: “Horizontal Banner Ad on ABC Order, the new product ordering and communication platform for AmerisourceBergen Drug Corporation customers.”³⁴¹
 - ii. In a 2012 document titled “McKesson Manufacturer Marketing” McKesson described ways it could increase sales of opioids and maximize profits for ACTIQ and FENTORA, by “delivering an unmatched combination of communication, promotion, distribution options, plus targeted analytics of exclusive data, McKesson will enable Cephalon to set strategies that prioritize opportunities, optimize resources, and maximize profitability. McKesson partners with pharmaceutical manufacturers such

³³⁴ JAN-MS-00864519 at -4521 (emphasis in original).

³³⁵ *Id.*, at 4522-4523. (emphasis in original)

³³⁶ Purdue Pharma Butrans Product Alert, September 2011, http://rphmail.com/ch/2011/butrans_101411.html. (last accessed Feb. 2., 2021)

³³⁷ ACTAVIS0375300 and ACTAVIS0375303; *see also* ALLERGAN_MDL_01198205 and ALLERGAN_MDL_01198203

³³⁸ ACTAVIS0237771; *see also* ACTAVIS0190235(Kadian “Save up to \$1,200” brochure)

³³⁹ ACTAVIS0237771 at -7775

³⁴⁰ *Id.*

³⁴¹ ABDCMDL00002828

as Cephalon to define and execute customized strategies targeting key awareness, sales, and distribution goals at all stages of the product life cycle.”³⁴² Cephalon was acquired by TEVA as of October 2011, shortly before McKesson prepared the “Manufacturer Marketing” proposal.³⁴³

- On January 25, 2012, McKesson partnered with TEVA to promote ACTIQ and FENTORA including an agreement to “distribute three (3) e-mail messages promoting the products identified below to 7,000 retail pharmacy recipients” and “four hundred sixty three (463) mailers to our top Independent Pharmacies.”³⁴⁴ The 2012 proposal and agreement between McKesson and TEVA demonstrates that McKesson was not just in the business of distribution but was actively engaged with manufacturers to find ways to sell more opioids.
- iv. Cardinal Health partnered with TEVA to promote TEVA products. Cardinal Health agreed to distribute, at Teva’s request, “one (1) e-mail communication to approximately 105,000 retail pharmacists and pharmacy technicians in Cardinal Health’s eConnection program database that includes information on the CII product launch.”³⁴⁵ And “The communication distributed by Cardinal Health will be prepared by Teva in accordance with the specifications set forth below.”³⁴⁶ Content “May include product benefits, ordering information and website links. Teva to provide the message to appear in the subject line of the email communication.” “The cost to distribute the above one (1) e-mail communication shall be Eighteen Thousand Dollars (\$18,000).”³⁴⁷
- Cardinal Health partnered with Actavis to promote Kadian through eConnection blasts urging retail pharmacists and pharmacy techs to “Stock up now, order today!”³⁴⁸ The Cardinal eConnection blasts were sent to approximately 98,000 pharmacists and pharmacy techs³⁴⁹ and were part of an Actavis stocking campaign to take advantage of supply shortages of Embeda, another long-acting opioid.³⁵⁰
- vi. McKesson Specialty Health Pharmaceutical & Biotech Solutions, LP, collaborated with Purdue Pharma to advertise Butrans Transdermal System in October 2016, for a fee of \$17,850. McKesson “agrees to post

³⁴² MCKMDL00353374 at -3376

³⁴³ Teva completed its acquisition of Cephalon on October 14, 2011, *see* <https://www.fiercepharma.com/pharma/teva-completes-acquisition-of-cephalon> (last accessed 10/22/2020)

³⁴⁴ MCKMDL00353368 at 3368.

³⁴⁵ CAH_MDL2804_00132726 at -2727.

³⁴⁶ *Id.*

³⁴⁷ *Id.*

³⁴⁸ ACTAVIS0220239, *see also* ACTAVIS00554311, http://rphmail.com/ch/2012/kadian_102312/printable.pdf, and CAH_MDL2804_02954370.

³⁴⁹ CAH_MDL2804_02958781 at -8782.

³⁵⁰ ACTAVIS0375300 and ACTAVIS0375303; *see also* ACTAVIS0357313 at -7320.

Supplier's graphical ad with a link to Supplier's Supplier Product website (<https://www.butrans.com>), on McKesson's online ordering portal, McKesson Connect. The graphical ad will be posted for a total of four (4) weeks."³⁵¹

- vii. AmerisourceBergen partnered with Purdue in 2008 to promote Oxycontin's "new items and the Rebate program".³⁵² AmerisourceBergen sent a mailing to over 5,500 retail accounts and an alert to AmerisourceBergen's retail group and customer service managers providing information regarding Purdue's "new OxyContin strengths available to ABC customers and the special rebate offer available to purchase these new items."³⁵³ The "rebate increases if you order multiple strengths" and discounts ranged from \$13-\$18 for each 15mg bottle to \$44-\$59 for each 60mg bottle of OxyContin.³⁵⁴
- viii. The opioid distributor Cardinal promoted Exalgo on pharmacy ordering platforms. As described in this email exchange between Cardinal executive Leslie Arend and Covidian executive Connie Kisinger on April 12, 2013, Cardinal's own legal team expressed reservations about ads promoting the opioid product Exalgo: "I received word late this morning that due to some things with the DEA, our legal team made several changes to marketing programs with controlled substances. While we can feature Exalgo on the ordering platform, it was deemed that it could only be prompted by a search key word of 'Exalgo'. The reason for this is legal has said that the pharmacist must actually be searching for the product in order to show the advertisement otherwise it may seem as though Cardinal Health is 'pushing' a controlled substance."³⁵⁵
- d. Opioid manufacturers and distributors worked together with pharmacies to market specific opioids at the pharmacy counter. Pharmacists were trained to influence patient demand under the guise of education and "medication adherence."³⁵⁶
 - In 2012, McKesson proposed that Janssen "enhance" its Nucynta free and discount pill programs by going directly to customers using face to face Motivational Interviewing at the "pharmacy counter."³⁵⁷ Motivational Interviewing is a form of individual psychotherapy originally conceived to

³⁵¹ MCKMDL00353277

³⁵² PPLPC004000146529 at -6530.

³⁵³ ABDCMDL07337446

³⁵⁴ ABDCMDL07337447 at -448

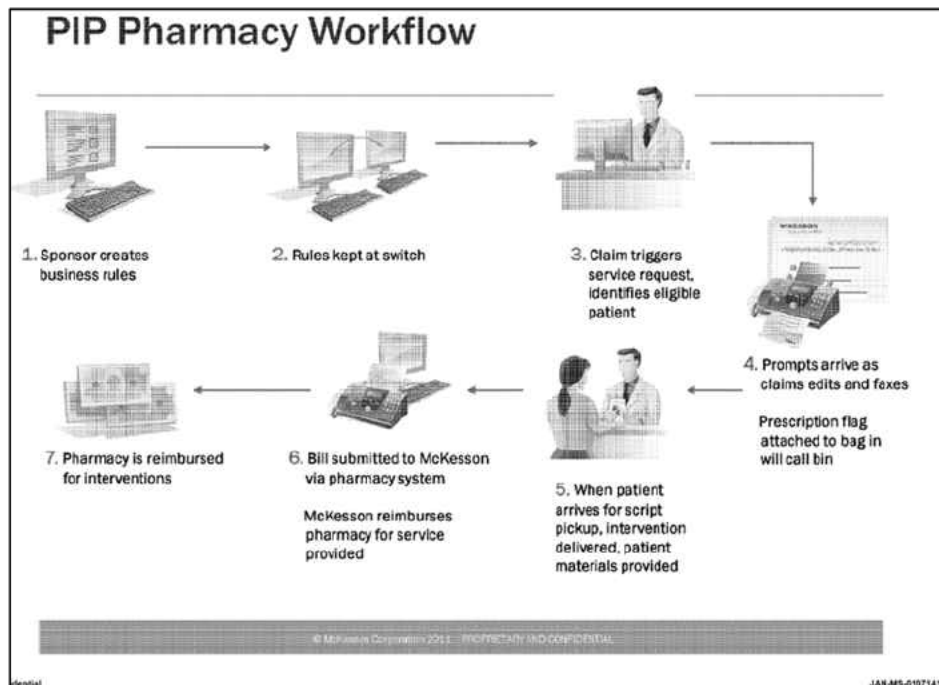
³⁵⁵ MNK-T1_0007819281

³⁵⁶ Rollnick S, Miller W. What is Motivational Interviewing? *Behavioural and Cognitive Psychotherapy*. 1995;23(4):325-334.

³⁵⁷ JAN-MS-01071368 at -1411-1416. McKesson implemented a similar program for Purdue's Butrans, see discussion at Section §C.5.e below.

help addicted patients get into recovery. It is ironic that McKesson recommended using these techniques to *encourage* opioid consumption.

- ii. McKesson's Pharmacy Intervention Program's stated goal was to "Increase patient adherence to prescribed drug therapy through a series of targeted 'behavioral modification' counseling sessions delivered at the pharmacy counter"³⁵⁸ and a "Comprehensive McKesson team assembled to support pharmacy execution."³⁵⁹ The pharmacies, in turn, would be reimbursed for doing MI at "the pharmacy counter." "McKesson reimburses pharmacy for service provided."³⁶⁰ The below McKesson slide shows how the Pharmacy Intervention Program ("PIP") worked³⁶¹:



- e. As stated by Lamkin and Elliott, "Of course, pharmaceutical adherence programs are not geared toward promoting patient health, but toward ensuring patients keep using a particular drug. As market research consultants Frost & Sullivan have acknowledged, 'The most compelling reason to invest in these tailored communications is to increase return on investment (ROI) by keeping patients on the therapy longer.' McKesson Patient Relationship Solutions assures pharmaceutical companies that the company's 'adherence tactics' will 'optimize the performance of your brand.'"³⁶² I agree with this view that pharmaceutical

³⁵⁸ *Id.*, at -1416.

³⁵⁹ *Id.*

³⁶⁰ *Id.*, at -1416-1417.

³⁶¹ *Id.*, at -1417.

³⁶² Lamkin M, Elliott C. Curing the disobedient patient: Medication adherence programs as pharmaceutical marketing tools. *Journal of Law, Medicine and Ethics*. 2014:492-500, at pp. 498-499.

adherence programs are geared to increasing ROI and brand optimization, rather than promoting patient health. With respect to prescription opioids, chronic adherence conferred far greater risks than benefits, and such adherence harmed, rather than promoted, patient health.

- i. Branded content was camouflaged inside non-branded “educational” content in the context of Motivational Interviewing. “Pharmacy Training/Support” including “Motivational Interviewing CE Coursework,” was paired with “Brand Specific Kit Contents” which included the following statement: “Manufacturer sponsors may elect to provide a piece of branded patient collateral.”³⁶³ See below a graphic of the pharmacy Motivational Interviewing intervention:

Pharmacy Training & Support

- **Pharmacy Training/Support**
 - *Brand agnostic, provided to all participating pharmacists*
 - **Motivational Interviewing CE Coursework:**
 - Developed by Motivational Interviewing expert Cethy Cole, this required training provides pharmacists with a foundation in the principles of Motivational Interviewing and health behavior change.
 - **Program Kit:** Focuses on the clinical and operational aspects of the program. Provides pharmacy staff with workflow training and support tools along with additional background information on Motivational Interviewing.
 - **Adherence Advisor:**
 - Monthly adherence newsletter distributed exclusively to Patient Outreach Network pharmacies.
 - **PON Call Center Team:**
 - Dedicated inbound and outbound team of expert callers who provide support for PIP pharmacies.
- **Brand Specific Kit Contents**
 - *Delivered to pharmacies prior to launch of a new brand*
 - **Product Kit Cover Letter:**
 - Provides overview of materials included in brand kit. Features brand specific program information, counseling tips and information about adverse event reporting.
 - **Pharmacist Consultation Aid**
 - This laminated one page guide provides brand specific information to guide the adherence counseling session.
 - **Product-Specific Clinical Information**
 - Manufacturer sponsors may elect to provide a piece of branded patient collateral

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- ii. In 2013, McKesson promoted its Pharmacy Intervention Program by letting Purdue know about their “Pharmacy Brand Kit,” whereby Purdue could promote its product under the guise of education: “The Brand Specific Pharmacy Kit is mailed to each participating pharmacies [sic] prior to launch. This kit includes a Cover Letter and Coaching Guide. Purdue will have the opportunity to participate in the development and review all pharmacy materials specific to their program. The brand kit can also include any additional resources the pharmacist should read as well as patient brochures to hand out during the coaching session (Purdue would develop and provide).”³⁶⁴

³⁶³ JAN-MS-01071368 at -1419.

³⁶⁴ PPLPC002000140782 at -0783.

- In other words, McKesson's Pharmacy Intervention Program was a vehicle for opioid manufacturers to advertise their products directly to patient consumers through pharmacists.
- iv. McKesson proposed to use its Pharmacy Intervention Program to increase opioid doses and thwart a trend they observed in 2013 in which patients were discontinuing opioids.³⁶⁵ McKesson promoted maintaining and even increasing doses of Butrans: "In 2013, one of our commercial goals is to reduce discontinuation and improve patient adherence.... HCPs are initiating opioid-experienced patients inappropriately on the 5 mcg/hour when they should be initiated on the 10 mcg/hour. These factors are negatively impacting patient adherence, and Marketing would like to execute the McKesson Pharmacy Intervention Program in order to reduce the Butrans discontinuation rate."³⁶⁶ As of April 2014, more than 675 Butrans PIP coaching sessions had been delivered to patients.³⁶⁷ Many patients on opioids at this time had good medical reasons for discontinuing opioids, including adverse medical consequences and serious risk of addiction and overdose death. Instead manufacturers, distributors, and pharmacies used "improving patient adherence" as a proxy for maintaining opioids.
- f. I am familiar with the reports of Craig McCann and James Rafalski on the subject of opioid distributors and red flags indicating on-going diversion.³⁶⁸ It is particularly persuasive that distributors and pharmacies such as McKesson, AmerisourceBergen, Cardinal, CVS, Walgreens and others have paid millions in settlements indicating their diversion systems failed.³⁶⁹ Rafalski's conclusions are consistent with my own opinions based on my review of the documents described above, that is, the Opioid Distributors collaborated with manufacturers and pharmacies to increase sales and patient exposure, while failing to implement meaningful systems to monitor or control rampant diversion and oversupply of opioids.

6. Pharmacies leveraged their unique and pivotal position in the opioid supply chain to contribute to the unprecedented and unchecked flow of opioid pain pills into the community. They alone had direct contact with opioid manufacturers and distributors upstream, and patients and prescribers downstream. Their coordinated efforts to "create demand" included advertising specific opioid products at the pharmacy counter, building

³⁶⁵ PPLPC002000140782

³⁶⁶ *Id.*

³⁶⁷ PPLPC017000552799

³⁶⁸ Expert Report of Craig J. McCann, *City of Huntington, West Virginia et al. v. AmerisourceBergen Drug Corporation et al.*, Case No. 3:17-01362 (Aug. 3, 2020). (hereinafter "McCann report"); Expert Report of James Rafalski, *City of Huntington, West Virginia et al. v. AmerisourceBergen Drug Corporation et al.*, Case No. 3:17-01362 (Aug. 3, 2020). (hereinafter "Rafalski Report")

³⁶⁹ Rafalski Report, at pp. 23-34. See also Section 6 of this report below, addressing fines and penalties imposed on Pharmacy Defendants for violations of the CSA.

opioid “Super Stores” to enhance unrestricted flow of opioid pain pills, spreading misinformation about the safety and efficacy of opioid pain pills, partnering with pro-opioid industry advocacy and lobbying organizations, ignoring “red flags” for misuse and diversion including concerns expressed by their own pharmacists, failing to provide pharmacists with sufficient time, resources, or incentives to investigate red flags, and failing to use or analyze their own dispensing data to assist pharmacies in identifying red flags. By increasing and assuring the supply of opioids and failing to provide effective controls against diversion, pharmacies contributed to opioid misuse, addiction, dependence, and death.

- a. Pharmacies occupy a unique and pivotal position in the opioid supply chain
 - i. Pharmacies, unlike other defendants in this litigation, had regular and direct contact with upstream and downstream suppliers (manufacturers, distributors, and prescribers) as well as face-to-face contact with patients themselves. As such, they were in the unique position of influencing the opioid supply chain at every level, from the corporate to the individual.
 - ii. The unique and influential role that pharmacists play today is well-captured by Lamkin and Elliott’s article on the role of pharmacies as marketing tools: “Like nurses, pharmacists have become ‘a key cog in not only the pharmaceutical chain, but also in the marketing of prescription drugs and services.’ Pharmacists are effective at improving adherence because patients trust them, ranking pharmacists second only to nurses in terms of professional ethics and honesty. In addition, patients interact more with pharmacists than any other health care professional. So pharmacists have many opportunities to influence patients and identify the reasons individual patients are not taking their medications. As pharmaceutical distributor McKesson says, pharmacists can offer ‘personalized messaging, program enrollment, behavioral coaching and other clinical services at the point of dispensing.’”³⁷⁰
 - iii. The CDC has stated that because pharmacists are “[o]n the front lines of dispensing opioid pain medications and providing medication-related services, pharmacists can serve as a first line of defense by engaging in prevention and treatment efforts of opioid use disorder and overdose.”³⁷¹
 - iv. Pharmacists and pharmacies have information that physicians don’t have concerning “red flags,” including but not limited to the following: a patient who pays in cash for the prescription, travels a far distance to fill a prescription, fills multiple prescriptions simultaneously for the same or similar drugs, fills multiple prescriptions that are dangerous in combination (opioids with benzodiazepines, and/or the “holy trinity” i.e.

³⁷⁰ Lamkin, *supra*, at 495, fn. 362(internal citations omitted)

³⁷¹ Centers for Disease Control and Prevention. Pharmacists: On the front lines. (Oct. 17, 2016), https://www.cdc.gov/drugoverdose/pdf/pharmacists_brochure-a.pdf (last accessed Jan. 15, 2021)

opioids, benzodiazepines, and muscle relaxants or other central nervous system depressants), and/or appears under the influence of an intoxicant at the time of filling.³⁷² The Pharmacy Defendants in this case also had access to their own chain-wide prescribing data that could have been analyzed to identify prescriber-related red flags that could have prevented substantial diversion, such as repeatedly combining dangerous medications, prescribing excessive doses, and prescribing outside of legitimate medical indications or not in the usual scope of clinical practice. Pharmacists and pharmacies have a duty to patients and the public interest to act on that information. They are also required to do so by the Controlled Substances Act.

- Trust in pharmacies is misplaced when their actions are directed at increasing return on investment rather than patients' legitimate medical needs.
- b. Pharmacy Defendants advertised specific opioid products, higher doses, and longer duration at the pharmacy counter
 - i. In 2011 CVS published an “educational services” document describing a promotional campaign they could launch within CVS Caremark pharmacies on behalf of selected opioid manufacturers, for a fee.³⁷³ This document illustrates that CVS Caremark was in the business of promoting opioids, not just dispensing them.
 - ii. The 2011 CVS document leads with the statement “Communicate your product’s unique clinical benefits to thousands of targeted individuals.”³⁷⁴ On the second page of this document, next to a picture of a pharmacist talking to two patient consumers, the document reads, “Get the medicine Right with the right educational communications.”³⁷⁵
 - iii. This document illustrates how CVS Caremark employed tactics initially introduced by Purdue Pharma to promote opioid products using targeted endorsements to specific patients under the guise of education. CVS courted opioid manufacturers with promises of “[i]dentifying patients who may benefit from your product,” increasing “awareness of new treatments or therapies,”³⁷⁶ and a “Pharmacy Literature Display” to “[e]ducate patients via literature located adjacent to prescription counter.”³⁷⁷ CVS Caremark used buzzwords like “education,” and “literature” to give their

³⁷² WAGMDL00254700, at -4701-4702.

³⁷³ INSYS-MDL-000422516

³⁷⁴ *Id.*, at -2517.

³⁷⁵ *Id.*

³⁷⁶ *Id.*, at -2519

³⁷⁷ *Id.*, at -2522.

promotional efforts the sheen of science, without the substance of scientific accuracy.

- iv. CVS offered these services to opioid manufacturers for a fee. A newsletter to pharmacies cost \$40,000.³⁷⁸ Likewise, strategically placed information for patients “adjacent to prescription counter” cost \$220,000/mo for 7,300 store distribution.³⁷⁹ CVS also engaged in direct-to-consumer advertising: Patient direct mailers,³⁸⁰ and “messaging” printed directly on customer prescription receipts, cost \$10,000 setup fee and \$0.20/print to allow for “targeting by product, fill or refill number, disease state or demographic selectors.”³⁸¹
- v. Walgreens also offered promotional services to opioid manufactures for a fee. For a cost of \$25,000, Walgreens would send manufacturer-supplied “educational or detailing material” to approximately 26,000 Walgreens pharmacists in over 7,800 retail store locations via Walgreens’ web-based communications platform.³⁸²
- vi. Walgreens allowed Purdue sales reps to make calls on Walgreens Healthcare Supervisors who oversaw 70-100 retail stores.³⁸³ Walgreens engaged with other opioid manufacturers as well, “to provide pharmacist education material to their pharmacists through corporate coordination, including branded and unbranded resources to reach 27,000 pharmacists.”³⁸⁴ Furthermore the relationship was a quid pro quo. In return, Walgreens provided Purdue with data on OxyContin purchases “at the store level.”³⁸⁵
- c. Pharmacy Defendants mailed promotional material directly to patients and prescribers
 - i. Opioid manufacturers, including Purdue and Actavis, contracted with a company called Adheris for prescription adherence programs to be offered to retail pharmacy chains including defendants Rite Aid, Giant Eagle, Walmart for prescription opioids including Butrans and Kadian.³⁸⁶ The goal of these programs was to improve patient adherence and increase

³⁷⁸ *Id.*, at -2521.

³⁷⁹ *Id.*, at -2522.

³⁸⁰ *Id.*, at -2525.

³⁸¹ *Id.*, at -2524.

³⁸² ALLERGAN MDL_00993985

³⁸³ PPLPC014000362725, at p. 2740.

³⁸⁴ *Id.*

³⁸⁵ *Id.*

³⁸⁶ PPLP003358929 and ALLERGAN MDL_01890807.

overall length of therapy by providing patients “behavior-triggered refill reminders.”³⁸⁷

- ii. A 2013 agreement between Purdue and Adheris detailed a year-long “DirectAdhere program” for Butrans with a goal “to improve patient adherence by providing patients with education on Butrans, disease state information, and timely, behavior-triggered refill reminders.”³⁸⁸ The agreement notes that the program will be offered to the retail pharmacy chains in the “Adheris Pharmacy Network” which included Walmart and Giant Eagle.³⁸⁹ The agreement called for 72,520 letters mailed to an estimated 19,600 Butrans patients.³⁹⁰ The communications included a letter that: “...encourages patients to contact their physicians to determine whether another prescription is appropriate and/or provides the option to request that the pharmacist contact the physician on the patient’s behalf.”³⁹¹ Templates of the letters submitted for Giant Eagle’s approval had a Giant Eagle letterhead and optional language regarding the Butrans Savings Program, “The Butrans Savings Card allows eligible patients with a valid prescription for Butrans to save up to \$50 on each prescription after paying the first \$15.”³⁹²

■ “Approximately 6k pharmacies partnered with the Butrans DirectAdhere program” from Adheris, a direct-to-patient mail program including a Welcome Letter, an Enrollment Reinforcement Letter, Refill #1 Reminder Letter and a Next Rx Letter, that were mailed directly to the patient, at home, on the letterhead of their pharmacy.³⁹³ The Butrans DirectAdhere program had a 2:1 ROI [return on investment] guaranteed in the contract.³⁹⁴
- iv. “Actavis Kadian LLC” and “Adheris, an inVentiv health company”³⁹⁵ signed a 2009 agreement for a year-long adherence program to “improve patient persistence and increase the overall length of therapy by providing patients with education on [Kadian], tips to help manage pain, and timely, behavior-triggered refill reminders.”³⁹⁶ The agreement called for 37,500 projected letters mailed to an estimated 15,000 Kadian patients.³⁹⁷ The

³⁸⁷ *Id.*

³⁸⁸ PPLP003358929

³⁸⁹ *Id.* at 8933, 8936.

³⁹⁰ *Id.*, at 8932.

³⁹¹ *Id.*, at 8931.

³⁹² HBC MDL00160082 and HBC MDL00160083.

³⁹³ PPLPC017000552799.

³⁹⁴ *Id.*, at 2800.

³⁹⁵ Actavis also contracted InVentiv to employ a Kadian sales force. See §C4.b.v., above.

³⁹⁶ ALLERGAN_MDL_01890807

³⁹⁷ *Id.* at 0818.

program was to be offered to all the pharmacies in Adheris' pharmacy network which included Rite Aid, Walmart, and Giant Eagle.³⁹⁸

- v. A six month analysis of an Adheris "Kadian Adherence Program" showed "strong adherence improvements compared to control patients" with 5.3 incremental capsules obtained per Adherence Program patient, Adherence Program patients were 5.2% more likely to remain on therapy, and 1.4% more likely to return with new prescription.³⁹⁹
- vi. This adherence program, like the others, exposed greater numbers of patients to chronic opioids that conferred significant risks while conferring little, if any, benefit.
- d. Pharmacy Defendants built opioid "Super Stores" to enhance unrestricted flow of opioid pain pills
 - i. Pharmacies have claimed that because they dispense medications in response to a doctor's prescription, they are merely passive purveyors of opioid pain pills. But in fact, pharmacies played a pivotal role in driving demand. As the only entities that had direct contact with both prescribing doctors and patient consumers, pharmacies provided a critical link in the corporate supply chain and used this role to promote the supply of prescription opioids, thereby substantially contributed to the opioid epidemic.
 - ii. In a series of May 1997 emails to Purdue's Chesapeake District sales force, with the subject heading "OxyContin Super Stores!!"⁴⁰⁰ Purdue executives incentivized and coached sales representatives on how to create OxyContin Super Stores, the "pill mill" equivalent of chain pharmacies. Purdue's actions capitalized on the pivotal role that pharmacies and pharmacists played in promoting OxyContin.
 - iii. First, Purdue incentivized drug representatives to create OxyContin Super Stores by promising them a trip to London and a bonus: "OxyContin 80mg is your ticket to London. OxyContin 80mg is your ticket to bonus. OxyContin 80mg is crucial to your success. But, only if your doctors' patients can GET it!"⁴⁰¹ In other words, make sure the pharmacies are stocked with OxyContin.
 - iv. Among the "important notes" for Purdue sales reps was the following: "Call in this Friday morning with the number of 40 & 80mg stores you have stocked this week," and "Set up Super stores: Every

³⁹⁸ *Id.* at 0817, 0829.

³⁹⁹ ALLERGAN_MDL_00221533 at 1534.

⁴⁰⁰ PPLPC024000002380

⁴⁰¹ *Id.*

territory must have a MINIMUM of eight to twelve SUPER STORES identified and stocked.”⁴⁰²

- v. Purdue also offered “how to” advice to its sales reps, such as: “Ask your key doctors, nurses, clinics and hospices about specific patients on doses of more than one 40mg tablet q12h. Get them to switch the patients to 80mg tablets. Create the demand. Recognize the need. Arm yourself with this information. Use it to convince your pharmacies.... How many tablets are your 80mg patients taking? Some are taking 8 tablets!! You’ll lose that patient on the next titration.”⁴⁰³
- vi. Especially noteworthy here is the statement “Create the demand,” as it highlights the fact that opioid manufacturers sought the assistance of pharmacists and pharmacies to influence the numbers and types of prescriptions that were written.
- vii. March 2008 internal Purdue emails described a potential meeting with the “Big 3” distributors “to talk about DEA’s latest plans to squeeze the wholesalers and distributors on ‘pain clinics’... We really do have to partner with our own customers to help them in their business with pharmacies catering to ‘pain clinics’. Otherwise, they will cut them off based on some kind of threshold.”⁴⁰⁴ This email makes it clear that Purdue understood the importance of pharmacies catering to pain clinics as essential to their profit margin.
- viii. A July 2013 Purdue presentation on order monitoring and retailer due diligence included a reference to meetings with major pharmacies: “senior management at Walgreens, Rite Aid, Walmart.”⁴⁰⁵ After a summary of recent DEA actions against pharmacies related to diversion, Purdue detailed the “[o]rder [m]onitoring [i]mpact: [p]ossible reduction/limitation of supply.”⁴⁰⁶ Among the actions Purdue proposed was working “on a study to utilize with the trade on what an appropriate patient ‘looks like’”⁴⁰⁷ and “[e]nhanced pharmacist education” including “[b]road distribution of the OxyContin Pharmacist Guide.”⁴⁰⁸ Purdue concluded that “inventory across supply chain [was] decreasing.”⁴⁰⁹ Purdue was “hearing of overflow into stores who have inventory causing them to run

⁴⁰² *Id.*

⁴⁰³ *Id.*, at -2381.

⁴⁰⁴ PPLPC018000200323-0324

⁴⁰⁵ PPLPC004000363085 (produced natively), at *14.

⁴⁰⁶ *Id.*, at *2-6 and *9.

⁴⁰⁷ *Id.*, at *19.

⁴⁰⁸ *Id.*, at *20.

⁴⁰⁹ *Id.*, at *21.

out early and unable to obtain more product before the next months and next ‘allotment.’”⁴¹⁰

- ix. This document highlights the regular communications between Purdue and pharmacy executives. Further, it demonstrates that corporate leaders at all levels of the supply chain were aware of the risks associated with OxyContin diversion.
- x. Walgreens sought to make opioids readily available to the public by collaborating with opioid manufacturers and the distributor, Amerisource Bergen, and ignoring pharmacists’ important role as safe stewards of highly addictive opioids with a high risk of diversion.
- xi. A series of February 1997 internal Purdue emails regarding Walgreens pharmacy calls began with Purdue Sales rep Eric Perham writing to his colleague/manager: “Today was a great day for pharmacy calls!”⁴¹¹ The email then goes on to describe Perham’s conversation with Walgreens pharmacist Bob Brody.
- xii. Walgreens pharmacist Brody’s protocol recommendations included “the 24 hour stores increase there [sic] narcotic inventory as much as 8 fold to cover each area,” informing “high prescribers in the area that those stores will always have an adequate inventory,” that “These stores will also have well informed pharmacist in the area of pain management” to “eliminate any confusion on the ‘correct’ dose for the patient,” and finally, that these select, well-stocked pharmacies will have the added benefit that they will “save patients time from having to shop around for stores that carry the pain medications. The doctors will have the assurance that the pain meds will be filled by a pharmacist less likely to question his/her prescribing habits.”⁴¹²
- The summary depicts the pharmacist, Brody, as actively involved in not just promoting opioids but specifically OxyContin through development of a “‘simple’ pain management protocol at the pharmacy level”, including making sure that pharmacies always have OxyContin in stock, and discouraging pharmacists from questioning opioid prescriptions, denying them their critical role as safeguards against misuse and diversion.⁴¹³
- xiv. The Purdue sales manager Chris Sposalto responded to these suggestions with, “Great cccontact [sic]!!...While we are not in the business of promoting pharmacies per se, it is our obligation to our customers to direct them to locations that will (without a doubt) be carrying our OxyContin

⁴¹⁰ *Id.*

⁴¹¹ PDD8801156563 at -6564.

⁴¹² *Id.*, at -6564-6565.

⁴¹³ *Id.*, at -6564-6565.

line. You should inform these key Dr's, nurses, PA's, NP's, etc on your calls and have a list available near their phones so they can take action toward OxyContin prescriptions at a moment's notice."⁴¹⁴

- xv. According to a November 1999 Purdue memorandum, Bob Brody's planned protocol to promote OxyContin was successfully implemented by Walgreens.⁴¹⁵ The memorandum summarized continuing education-accredited presentations to pharmacists and stated that "One of the Walgreen's pharmacists (Bob Brody) got up at the beginning of each meeting and made a short presentation on his store and a program that they have implemented. His store actively advertises to area MDs and patients that they are a 'full-service' pain management pharmacy. This service includes providing a list to the physicians' offices of all CII they have in stock (and they have everything), accepting 'verbal orders' for Class II analgesics prior to presentation of the original prescription at the store to decrease 'waiting time', allowing partial fills on CII prescription in terminal patients, and accepting after hours 'emergency CII prescriptions' without a hassle. This pharmacist was fantastic."⁴¹⁶
- xvi. That Walgreens collaborated with Purdue is manifest by the remarkable sales of OxyContin at Walgreens pharmacies: "Walgreens distributes ~\$374M (16.8%) of Purdue's prescription products; Walgreens is the largest of the >200 retail chains that dispense Purdue Rx Products"⁴¹⁷
- xvii. Below is a chart showing the average monthly OxyContin sales at Walgreens from 2010 to 2017. OxyContin sales in 2010 continued to be at very high levels through 2017.⁴¹⁸

OxyContin				
Year	Avg. Monthly	Annualized	Annual Change	% Change
2010	\$25,269,202	\$303,230,419		
2011	\$33,828,465	\$405,941,577	\$102,711,158	33.9%
2012	\$34,247,556	\$410,970,670	\$5,029,093	1.2%
2013	\$28,203,503	\$338,442,039	(\$72,528,630)	-17.6%
2014	\$26,663,383	\$319,960,601	(\$18,481,439)	-5.5%
2015	\$27,760,433	\$333,125,200	\$13,164,599	4.1%
2016	\$27,714,597	\$332,575,162	(\$550,038)	-0.2%
2017	\$25,157,465	\$301,889,576	(\$30,685,586)	-9.2%

⁴¹⁴ *Id.*, at -6563-6564.

⁴¹⁵ PPLPC028000008080, at -8081.

⁴¹⁶ *Id.*

⁴¹⁷ PPLPC014000362725, at -2738

⁴¹⁸ *Id.*

- xviii. These documents further attest to Walgreens' role in assuring the widespread availability of opioids, and in promoting the specific product, OxyContin.
- xix. In 2008, Walgreens had an agreement with Purdue wherein Purdue agreed to replace OxyContin losses at a pharmacy due to theft or robbery.⁴¹⁹ Theft and robbery from pharmacies are a form of diversion. Replacing opioid pharmacy stock without increasing safeguards to mitigate diversion, does little to help the public good.
- xx. [REDACTED]
[REDACTED]
[REDACTED]⁴²⁰
- xxi. [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]²¹
- xxii. [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]²²
- xxiii. [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]²³
- xxiv. [REDACTED]
[REDACTED]
[REDACTED]

⁴¹⁹ PPLPC004000170570, at -0572.

⁴²⁰ [REDACTED]

⁴²¹ *Id.*

⁴²² *Id.*

⁴²³ *Id.*

[REDACTED]

[REDACTED]

[REDACTED]

- e. Pharmacy Defendants spread misinformation about the safety and efficacy of opioids
 - i. Pharmacies collaborated with opioid manufacturers and distributors to propagate myths about opioids, including overstating benefits and understating risks. Although they made efforts to educate pharmacists about risks of diversion, they focused on identifying the addicted “abuser,” rather than the much larger public health consequence of flooding the market with an oversupply of highly addictive opioids.
 - ii. On May 2, 2001 senior executives at Purdue met with “key pharmacy people at CVS.”⁴²⁵ The stated goal of the meeting was to “talk about mutually beneficial initiatives with CVS to improve education with their pharmacists. We also wanted to reiterate our position on ensuring availability of OxyContin for appropriate patients.”⁴²⁶ Note the use of the phrase “mutually beneficial initiatives,” illustrating the implicit quid pro quo which characterized many of these meetings between opioid manufacturers and pharmacies.
 - iii. A memorandum summarizing the meeting described that the “key pharmacy people” were “resolute in their commitment to good pharmacy practice,” which included “ensuring availability of OxyContin.”⁴²⁷ Also, “As a group they were vocal, particularly Barry Jasilli [CVS, Director, Quality Improvement], indicating that they felt that Purdue was in many ways being victimized by the situation. That the product is not the issue, but that the abuser is the issue. He indicated that, from his perspective, we should be fighting back even harder.”⁴²⁸
 - iv. In the meeting, CVS agreed to post Purdue’s Abuse and Diversion brochure on their intranet site and send copies with personalized letters to 4,100 CVS pharmacists. Further, they discussed their “joint educational efforts,” “setting up at least five programs at this time through CVS,” “co-hosting programs in the areas of healthcare professionals”, and “CE programs.”⁴²⁹

⁴²⁴ [REDACTED]

⁴²⁵ PDD1701046870.

⁴²⁶ *Id.*

⁴²⁷ *Id.*

⁴²⁸ *Id.*

⁴²⁹ *Id.*

- v. This memo unambiguously demonstrates that CVS cooperated with Purdue in their efforts to promote OxyContin, to depict the opioid epidemic as a problem of minority “abusers” rather than the more widespread problem of opioid oversupply, overdose fatalities, and addiction.
- vi. Further, CVS’s promotion of Purdue’s Abuse and Diversion brochure - “How to Stop Drug Diversion and Protect Your Pharmacy”⁴³⁰ - sidestepped the significant problem of patient consumers getting addicted through legitimate prescriptions. Contrary to Industry claims that addiction is “rare,” some 10-30% of chronic pain patients on long-term opioid therapy are addicted to opioids. Notably, it is telling that the document emphasized “how to ... protect your pharmacy” rather than focusing on how to protect patients.
- vii. A June 2001 letter to CVS pharmacists announced CVS’ participation in *Partners Against Pain*, sponsored by Purdue Pharma. The letter called Purdue “a leader in educating the healthcare community on effective pain management and the appropriate use of pain medicines.”⁴³¹ Purdue’s *Partners Against Pain* campaign used the same promotional tactics and misleading messages that Purdue has pleaded guilty to in federal court, including overstating the benefits and understating the risks of opioids prescribed for pain.
- viii. An excerpt from the *Partners Against Pain* website from March 2001, under the subheading “Barriers to Effective Cancer Pain Management: A Review of the Literature,” included the following: “The majority of physicians and nurses fear that opioid use will result in addiction, drug tolerance, and uncontrollable side effects, especially respiratory depression. They fail to differentiate between addiction and physical dependence and to recognize that a) the risk for addiction is low in patients with no history of substance abuse and b) that there is little or no tolerance to the analgesic effects of opioids. They often base opioid doses on the severity of disease or their own fear of drug tolerance rather than on the intensity and level of the patient’s pain. Many do not acknowledge the efficacy of opioids administered orally or antidepressants prescribed as adjuvants.”⁴³² This statement encapsulates many of the false and misleading messages about opioids promulgated by the Industry. In fact, the risk of addiction to opioid analgesics prescribed to a doctor is high. Tolerance to the analgesic effects of opioids is common and probably occurs in the majority of consumers. A patient’s subjective endorsement

⁴³⁰ PKY18028211

⁴³¹ PDD1501726314

⁴³² *Partners Against Pain* website (March 2001), https://web.archive.org/web/20010605165846/http://www.partnersagainstpain.com/html/profed/pmc/pe_pmc4.htm#barriers (last accessed December 14, 2020)

of pain should never be the sole criterion on which opioids are titrated, because dependent patients frequently cannot distinguish between the pain of opioid withdrawal and the pain of whatever condition led them to initiate opioid therapy in the first place.

- ix. Although the earliest date in the documents that I have seen linking CVS to the *Partners Against Pain* program is April 2001,⁴³³ the content of the material on the *Partners Against Pain* website after 2001 was similar to Purdue's earlier misrepresentations, including invalid terms such as "pseudoaddiction" and "pseudotolerance." The website repeatedly promoted the now discredited JCAHO mandates for "regular assessment of pain and the establishment of policies and procedures that support the appropriate use of pain medication" along with "educational materials developed by Purdue Pharma to help you comply with the JCAHO pain standards."⁴³⁴
- x. Purdue's Executive Director of National accounts and Trade Relations, Stephen Seid, testified regarding the June 2001 CVS/Purdue *Partners Against Pain* (PAP) letter.⁴³⁵ "First of all, as I remember, the letter was prepared – [CVS] agreed to do this, but the letter was prepared by [CVS]. It got reviewed, but it was their letter since it was on their letterhead.... So the goal was to build a better relationship with CVS, No.1"⁴³⁶ The letter was probably sent to "about 12,000 pharmacists and about 18,000 pharmacy techs."⁴³⁷
- xi. In August 2001, CVS wrote a letter to Purdue Pharma asking Purdue to fund an educational program they would deliver to pharmacists at their Marketing and Operations conference in Nashville, TN in September 2001.⁴³⁸ In describing their proposed educational plan, they emphasized pharmacists' "role change from one of a dispenser of products to that of a supplier of information, deliverer of medication, clinical reviewer of drug therapy, and even disease state manager."⁴³⁹ By virtue of this educational plan, CVS itself established that the pharmacists' role went well beyond that of passive pill dispenser.
- xii. CVS requested \$46,079 for the continuing education course for pharmacists,⁴⁴⁰ which would include role playing opportunities on "how to

⁴³³ See e.g., PKY180409814

⁴³⁴ Partners Against Pain website (June 2004), <https://web.archive.org/web/20040603003006/http://partnersagainstpain.com/index-mp.aspx?sid=7> and <https://web.archive.org/web/20040611091507/http://partnersagainstpain.com/index-hs.aspx?sid=22&aid=7795>

⁴³⁵ PDD1501726314; See also, PPLPC008000018733 (produced natively), at *46

⁴³⁶ Deposition of Stephen Seid (December 12, 2018), 119:19-120:11.

⁴³⁷ *Id.*

⁴³⁸ PPLPC008000019586, at 9587-9588.

⁴³⁹ *Id.*, at -9586.

⁴⁴⁰ *Id.*, at -9588.

handle situations which are often associated with Purdue's products. By way of example: how to communicate effectively with patients and physicians about appropriate pain management therapy and how to resolve potential conflict with a drug 'seeker'".⁴⁴¹ Further, the memo touted CVS' long history of having a positive relationship with Purdue, the benefits of the program to both organizations, and how the continuing education series would "contribute significantly to our strategic business goals."⁴⁴²

- xiii. CVS' memo reveals how well CVS understood the key role pharmacists play in influencing patients' interactions with prescribers, and how CVS's "strategic business goals" were linked to those of Purdue.

■ In a December 1998 letter to Walgreens Pharmacy Supervisor, Scott Diveney, R PH, Purdue offered to fund a Purdue-sponsored continuing education (CE) program for pharmacists entitled "Use of Opioids – A Pharmacists' Responsibilities."⁴⁴³ The offer was accepted.⁴⁴⁴

■ In an August 1999 letter to Walgreens Pharmacy Supervisor, Scott Diveney, R PH, Purdue offered to fund another Purdue-sponsored continuing education (CE) program for pharmacists entitled "Current Trends and the Pharmacist's Role in the Treatment of Chronic Non-Malignant Pain."⁴⁴⁵

- xvi. Purdue and other opioid manufacturers sponsored and funded continuing education programs for health care providers, including pharmacists, as a way to promote the paradigm shift toward opioids as a first-line treatment for minor and chronic pain conditions. The staple of these events included the misleading messages about opioids detailed in this Report, including overstating the benefits and minimizing the harms.
- xvii. At the invitation of a Walmart pharmacist, acting in his capacity of the President of the Treasure Coast (Florida) Pharmacist Association, Purdue sponsored and presented a continuing education program to that association in November 1999, entitled, "Use of Opioids in Chronic Cancer and Non-Cancer Pain Management: The Myths and Realities."⁴⁴⁶ The Purdue sales representative noted, "This program represents a huge opportunity for Purdue since 100 pharmacists from the Treasure Coast area of Florida will be in attendance. Pharmacists from retail and hospital pharmacies (including Hospital Pharmacy Directors and retail pharmacy managers) in the Treasure Coast area (which includes the area from

⁴⁴¹ *Id.*, at -9586

⁴⁴² *Id.*

⁴⁴³ PKY180836236

⁴⁴⁴ See signed agreement at PKY180836239.

⁴⁴⁵ PKY180524065

⁴⁴⁶ PKY180512514 at 2515

Sebastian to Jupiter, FL) are members of the association. This lecture will not only be key in educating pharmacists on the role of opioids in pain management and why OxyContin (and Palladone XL) are the best choices of opioid analgesics, but also improving the potential of Palladone XL⁴⁴⁷ being placed on area hospital formularies.”⁴⁴⁸

- xviii. This document not only illustrates that Purdue promoted OxyContin by ‘teaching’ pharmacists that “OxyContin (and Palladone XC) are the best choices of opioid analgesics;” it further demonstrates the critical role that hospital formularies played in promoting certain opioid products. Once a drug is on a hospital formulary, it becomes the go-to drug for the high volume of opioids used within hospital systems. This top-down impact on large integrated health care systems cannot be overestimated. Hospitals and health care systems are training grounds for residents and medical students. It is well known within the medical profession that the skills and practices students and residents learn during their training, are the habits they take with them out into the world, wherever they end up practicing. Hence, hospital formularies have a lasting impact on how and what doctors prescribe.
- xix. An April 27, 2001 Purdue memo summarized a meeting between Purdue’s Senior Director of National Accounts and Trade Relations, Stephen Seid, and Sheila Bennett, Walgreen’s Category Manager Pharmacy Health and Wellness.⁴⁴⁹ The memo made it clear that Walgreens’ Bennett was an active participant in Purdue’s efforts to promote OxyContin, not a passive recipient of their promotional campaign. She offered her own original ideas to help support Purdue’s efforts to sell more OxyContin. Further, she shied away from actions that might decrease sales, even when those actions appropriately highlighted the risks of opioids.
- xx. In describing his conversation with Walgreens’ Sheila Bennett, Seid wrote, “Sheila, and Walgreens, are very strong in their resolve that the stores are expected to stock what they have in the warehouse. She indicated that this was policy approved by the Chairman of the Board. They are very strong on this philosophy. She also indicated that *we will work with you, as much as we can, so that patients get what they need.*”⁴⁵⁰
- xxi. During their discussion of educational efforts targeting pharmacists, “Sheila volunteered the fact that it is much wiser for us, and cost effective,

⁴⁴⁷ Palladone was a Purdue hydromorphone product that was removed from the market by agreement with the FDA, because of a high risk of mortality with even small amounts of alcohol that caused its opioid dose to be administered in a short time. See Peck, P., “FDA, Maker Agree to Pull Palladone Pain Killer.” MedPage Today, (July 15, 2005). <https://www.medpagetoday.com/primarycare/preventivecare/1364>

⁴⁴⁸ PKY180512514 at 2519.

⁴⁴⁹ PKY180267742 at 7742.

⁴⁵⁰ *Id.* (emphasis in original)

to do, what she called, Regional Level Market Programs. She indicated that instead of getting 30 or 40 pharmacists at a time, a Market Program should get 250-300 and address a market as opposed to just one district.”⁴⁵¹

- xxii. In other words, Walgreens’ executive Sheila Bennett was giving Purdue executive Stephen Seid inside information on how Walgreens trains its pharmacists, allowing Purdue to reach a larger target audience than it otherwise would have.
- xxiii. When Purdue executive Stephen Seid recommended that Walgreens find a way to disseminate Purdue’s “Abuse and Diversion Brochure,” Walgreen’s Bennett “expressed some concern that distributing this would scare people off of CIIIs [schedule II opioids]. She said, once again, that she would encourage, at the store level, that they stock and dispense OxyContin.”⁴⁵² That Bennett was reluctant to disseminate the brochure for fear it would “scare people off” is consistent with under-representing the true risks of opioids in order to promote consumption. Bennett should have been worried that people weren’t scared enough, especially as the opioid epidemic was unfolding around them.
- xxiv. Seid and Bennett discussed the problem of diversion of OxyContin and specifically the suspended distribution of OxyContin 160mg,⁴⁵³ the equivalent of 16 Percocet in a single pill, putting patients at high risk of addiction. Bennett was “concerned about the message it sent to the trade and the public.”⁴⁵⁴ Although the exact nature of her concern was not characterized, we can infer that she was concerned that suspending distribution of OxyContin 160mg would ‘scare off’ customers. She then offered her own suggestions about “tracking of OxyContin 160mg and make it less attractive for diversion, i.e. selling it in smaller quantities.”⁴⁵⁵ That Bennett, a Walgreens executive, was offering suggestions about how to reinstate OxyContin 160mg, speaks to the active and collaborative role Walgreens’ took to help Purdue promote OxyContin.
- xxv. The memo further reveals that Walgreens, based on its own data, which it shared with Purdue and is reproduced below, was able to see that as the dose of OxyContin tablets went up, so too did the number of pills dispensed.⁴⁵⁶

⁴⁵¹ *Id.*, at -7743.

⁴⁵² *Id.*, at -7742.

⁴⁵³ *Id.*, at -7743-7744.

⁴⁵⁴ *Id.*, at -7744.

⁴⁵⁵ *Id.*

⁴⁵⁶ *Id.*, at -7745.

Average Prescription Size and Number of Prescriptions Written

STRENGTH	NUMBER OF PRESCRIPTIONS	AVERAGE PRESCRIPTION SIZE
OxyContin 10mg	17,046	60 Tablets
OxyContin 20mg	26,517	65 Tablets
OxyContin 40mg	17,556	71.9 Tablets
OxyContin 80mg	6,413	80.9 Tablets
OxyContin 160mg	510	79.8 Tablets

- xxvi. This alone should have been cause for concern, since studies clearly show that the higher the dose and quantity of opioids, the greater the risk of addiction. Escalating doses of prescription opioids over time directly correlated with rising opioid deaths.
- xxvii. Instead, Stephen Seid interpreted these data as follows: “It is interesting to note that as the strength escalates, so do the number of tablets. It is also interesting to note that based on appropriate titration these numbers are very reasonable. This underscores the fact that the vast majority of OxyContin scripts appear to be written and dispensed appropriately.”⁴⁵⁷
- xxviii. The individual who wrote this memo, Stephen Seid, was honored in 2015 by the distributor’s trade/lobbying association with the “Distribution Management Award for Industry Leadership”, citing his work at Purdue “educat[ing] retail pharmacy networks and distributors on minimizing drug diversion and opioid abuse.”⁴⁵⁸
- xxix. A July 1996 document detailed a Purdue-sponsored continuing education program for Walmart pharmacists entitled “New Trends in the Use of Opioids in Pain Management.”⁴⁵⁹ Purdue paid Walmart \$20,000 in “educational grants” for this program.⁴⁶⁰ Presenters received honoraria for \$1,000.⁴⁶¹ The program was expected to reach 2,125 stores with 200-300 live attendees and 500 remote viewers.⁴⁶²
- xxx. The “New Trends” course program, which was delivered to Walmart pharmacists and elsewhere, was replete with misleading messages about opioids, taught by individuals who were on Purdue’s speaker bureau and

⁴⁵⁷ *Id.*⁴⁵⁸ Healthcare Distribution Alliance, “HDMA recognizes former Purdue Pharma executive Stephen Seid with Distribution Management Award for Industry Leadership” (March 10, 2015) <https://www.hdma.org/news/2015-03-10-hdma-recognizes-seid-with-dma-for-leadership>⁴⁵⁹ PKY180257493⁴⁶⁰ PKY180794346, at -4346.⁴⁶¹ *Id.*, at -4353-4354⁴⁶² *Id.*, at -4346.

receiving consulting fees from opioid manufacturers.⁴⁶³ Neil Irick, MD, one of the presenters of the “New Trends” CME to Walmart pharmacists was on Purdue’s Speaker’s Bureau, which means he had been trained by Purdue on course content and paid to deliver that content.⁴⁶⁴

xxxi. For example, in 1997 Neil Irick again presented on “New Trends for the Use of Opioids in Pain Management.” In that lecture, also sponsored by Purdue, Irick said that the best way to treat pain was to “[r]ealize that drugs and doctors do not cause drug addiction” and “[a]dmit that true addiction is much less of a problem than presumed.”⁴⁶⁵ By minimizing the risks of opioids and iatrogenic addiction, Irick’s message represented a radical departure from evidence and practice prior to 1990

xxxii. Arthur Lipman was a Professor at the College of Pharmacy and Pain Management Center at the University of Utah, and editor of the Journal of Pharmaceutical Care in Pain & Symptom Control, and a Purdue KOL who also conducted speakers training for nurses and pharmacists to be speakers on pain management.⁴⁶⁶ Because of his credentials in the pharmacy field, Lipman had particular credibility as a pharmacy expert. One example of Lipman’s training for pharmacists in 2000 stated: “Myth: Opioids Cause Addiction, Dependence and Tolerance; These effects can occur; They are rare in patients who have pain due to physiological causes.”⁴⁶⁷ In cases of “pseudoaddiction” Lipman recommended, “increase the opioid dose by 50%; assure that breakthrough doses are available.”⁴⁶⁸ Lipman estimated the prevalence of iatrogenic addiction in the range of 0.12% - 0.03%.⁴⁶⁹ In conclusion, Lipman urged his audience of nurses and pharmacists to “Refute Myths About Opioids” and stated that “addiction is exquisitely rare.”⁴⁷⁰ In fact, the best and most reliable estimates show that the risk of addiction to opioids is 10-30% among patients treated for chronic pain, as discussed in Section §C.8.b-c, below.

xxxiii. A series of internal Purdue emails from June 2000 touted a “COMPLETE Value-Added Program...to better educate pharmacists on proper pain management.”⁴⁷¹ Purdue’s sales representative “worked contacts at Giant Eagle [a 150 store chain] to initiate a mailing of 550 Lipman CEs [continuing education program materials] to the chain’s retail pharmacies.”⁴⁷² Purdue’s email described this program as a “win-win” for

⁴⁶³ PKY180960389, at -0389-0395

⁴⁶⁴ PKY180257493; PKY180960389 at -0394.

⁴⁶⁵ PKY180960389 at -0410.

⁴⁶⁶ PKY181218532, at 8533.

⁴⁶⁷ *Id.*, at 8535.

⁴⁶⁸ *Id.*, at 8536

⁴⁶⁹ *Id.*

⁴⁷⁰ *Id.*, at 8545

⁴⁷¹ PPLPC029000019201 at 9202.

⁴⁷² *Id.*

the customer and Purdue, which advanced the sale of Purdue Products “while educating the healthcare professional,” and helping “either (or both) the PSD [Prescription Sales Division] or HSD [Hospital Specialty Division] sell more of our products.”⁴⁷³ These Purdue sponsored continuing education materials provided misinformation to pharmacists concerning the false assertions of the low risk and great benefits of opioids, with the cooperation of Pharmacy Defendant Giant Eagle. Later emails endorsed these programs, with one Purdue sales executive noting that “The absolute last thing we want is for the OxyContin prescription to be bounced out at the pharmacy level because of unfounded fears from the ‘uneducated’ pharmacist.”⁴⁷⁴

xxxiv. A 2012 on-line CE for pharmacists “Navigating the Management of Chronic Pain: A Pharmacist’s Guide” was sponsored by Endo and available through the “CE Search Engine.”⁴⁷⁵ Endo’s CE stated that full agonist opioids “have a potentially unlimited dose response and, thus, a theoretically unlimited dosing ceiling. In practice, however, patients often experience significant adverse effects as opioid doses increase. (Table 2).”⁴⁷⁶ Table 2 lists significant adverse effects as constipation, nausea/vomiting, sedation/mental clouding and agitation/confusion⁴⁷⁷ while failing to mention or list perhaps the most significant adverse effect of all: the significantly increased risk of addiction and death that comes with higher doses.

xxxv. Further, the Endo CE noted that “[i]n a departure from previous guidelines, The American Geriatrics Society (AGS) now recommends a trial of opioids be considered for older patients with moderate-to-severe pain.”⁴⁷⁸ What the CE did not note, however, was that the American Geriatrics Society received \$6,500 from Endo in 2000 alone and more than \$1.3 million from Endo, Purdue and Johnson & Johnson from 1997-2012.⁴⁷⁹

xxxvi. Endo’s CE to pharmacists went on to introduce the term “opiophobia” to describe the “various fears and prejudices associated with the use of opioid analgesics which seems to unnecessarily limit the use of this class of medication,” and recommended that “A good understanding of terms such as pseudoaddiction and pseudotolerance will assist clinicians with educating colleagues and patients about the proper use of these

⁴⁷³ *Id.*; PPLPC010000016612.

⁴⁷⁴ PPLPC029000019201 at 9201.

⁴⁷⁵ WAGMDL00766955

⁴⁷⁶ *Id.*, at -6962.

⁴⁷⁷ *Id.*

⁴⁷⁸ WAGMDL0076695, at -6962.

⁴⁷⁹ US Senate Finance Committee, “Findings”, fn. 258, above, at Appendix A.

analgesics.”⁴⁸⁰ (see discussion of ‘pseudoaddiction’ at Section §C.4.k, above).

- f. Pharmacy Defendants partnered with pro-opioid industry advocacy and lobbying organizations
 - i. Pharmacies joined together with the The National Association of Chain Drug Stores (NACDS) and the Pain Care Forum, “a loose coalition of drugmakers, trade groups and dozens of nonprofits supported by industry funding,”⁴⁸¹ to disseminate pro-opioid messages, even amidst a growing opioid epidemic in Ohio and beyond. Between 2006 and 2015 the Pain Care Forum spent more than \$880 million on campaign contributions and lobbying expenses to promote their opioid agenda, including millions of dollars in Ohio alone.⁴⁸²
 - ii. The NACDS/Pain Care Forum opioid agenda included shifting media coverage away from the opioid epidemic to focus instead on maintaining access to opioids. “As you may recall, NACDS spearheads the communications working group of the Pain Care Forum. As a group we have been working to tell the story in the media of the unintended consequences that legitimate patients face when they cannot access prescription drug medications. Often times, the media focus just on abuse in their coverage.”⁴⁸³
- The NACDS/Pain Care Forum efforts included developing a “microsite” on Drug Store News featuring interviews with patient advocates.⁴⁸⁴ These interviews included false and misleading pro-opioid messages about opioid misuse and addiction.⁴⁸⁵
 - A. According to an October 2014 article titled “The Other Side of the Pain Medication Debate-Legitimate Patients” and still active on the NACDS website, the purpose of the microsite was to “help bring attention and reduce the stigma Americans who live with chronic pain often experience. The site puts a face on these legitimate patients and what it means when they are unable to access the medications they need to manage pain...heightened awareness in the media about the often untold side of the

⁴⁸⁰ WAGMDL00766955, at -6962-6963.

⁴⁸¹ Matthew Perrone, Ben Wieder, “Pro-Painkiller Echo Chamber Shaped Policy Amid Drug Epidemic” Public Integrity (Dec. 15, 2016), *see* “<https://publicintegrity.org/politics/state-politics/pro-painkiller-echo-chamber-shaped-policy-amid-drug-epidemic/>

⁴⁸² Associated Press and the Center for Public Integrity, Politics of Pain: A decade of opioid lobbying (2016), http://data.ap.org/projects/2016/cpi_ap_opioids/indexcpiap.html

⁴⁸³ WAGMDL00590913, at -0917.

⁴⁸⁴ *Id.*, at -0916.

⁴⁸⁵ Microsite archived at: <http://web.archive.org/web/20140712213014/http://www.drugstorenews.com/pain-management-2>

prescription drug abuse story is an important advancement that highlights the unintended victims of the debate - patients who legitimately need medications.”⁴⁸⁶ This messaging created a false dichotomy between “legitimate pain patients” and those who become addicted to prescription opioids, when in fact they are all too often one and the same. As noted at Section §C.8 of this report, approximately 21-29% of patients taking opioids “legitimately” prescribed by their physicians for chronic pain have an opioid use disorder.

- B. Other NACDS/Pain Forum statements include: (i) “But the media focus has historically been on the addicts and how to curtail their access to the pain medicines they crave. That creates a real stigma that inhibits access for legitimate patients from doctors to pharmacists to the patients themselves;”⁴⁸⁷ and (ii) “[w]hile the number of patients who have a legitimate need for prescription painkillers — 100 million plus — is vastly more than the number of people addicted to painkillers — 11 million — there is a stigma attached to the prescribing, dispensing and utilization of pain medicines. And that stigma has created an, [sic] at times, insurmountable hurdle that leaves legitimate patients suffering in silence.”⁴⁸⁸ Invoking the Institutes of Medicine statistic regarding the prevalence of pain in the United States – 100 million, falsely conveys that every American with pain needs opioids. In fact, far less than the 100 million Americans cited in the IOM report have pain severe enough to warrant any medical intervention; and among those who do, opioids are appropriate for only a very small minority.⁴⁸⁹

- iv. An NACDS representative wrote in an email in 2013, “With respect to DEA, last year the NACDS Board directed us to convene a Task Force to develop policies and a strategy to push back on DEA’s aggressive tactics

⁴⁸⁶ Lisa Boylan, *The Other Side of the Pain Medication Debate: Legitimate patients*. NACDS.org, Oct. 2, 2014 (last accessed January 28, 2021). See: <https://www.nacds.org/news/the-other-side-of-the-pain-medication-debatelegitimate-patients/>

⁴⁸⁷ Michael Johnsen, *Chronic Pain Sufferers Advocate Against Sigma of Prescription Pain Meds*, May 29, 2014 (last accessed January 28, 2021). See:

<http://web.archive.org/web/20140703054325/http://www.drugstorenews.com/article/chronic-pain-sufferers-advocate-against-stigma-prescription-pain-meds>

⁴⁸⁸ *Id.*

⁴⁸⁹ See Appendix IV to this report, citing a recent NIH study reporting that “High Impact Chronic Pain,” defined as the experience of pain on most days over the past 3 months, with concomitant limitations on activities due to pain, is experienced by 4.8% of US adults, or about 10.6 million people—about 1/10th of the “100 million” figure erroneously relied on by defendants to exaggerate the need for opioid pain treatment.

including expecting pharmacies to be policemen.”⁴⁹⁰ Pharmacies, acted through the NACDS Board that directed such a Task Force be convened.

- A. The Task Force made it part of their mission to “draft a letter to the Hill” regarding hydrocodone scheduling.⁴⁹¹ For nearly a decade the Department of Justice advocated up-scheduling hydrocodone products from Schedule III to Schedule II, providing an additional layer of protection against misuse and diversion. Instead of supporting this initiative, which was ultimately approved, pharmacies working with NACDS and the Pain Care Forum lobbied against it. “We are also working with the patient groups to advocate that FDA not recommend rescheduling these products.”⁴⁹²
- B. Pharmacies’ efforts against rescheduling hydrocodone provide another example of their contribution to the problems of opioid oversupply, misuse, addiction, and death, and their failure to work with other regulatory agencies to stem the tide of the opioid epidemic.

■ [REDACTED]

■ [REDACTED]

⁴⁹⁰ Rite_Aid_OMDL_0027468

⁴⁹¹ *Id.*

⁴⁹² *Id.*

■ [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]

■ [REDACTED]

[REDACTED]

[REDACTED]

- g. Pharmacy Defendants failed to adequately respond to “red flags” for misuse and diversion or support individual pharmacists in these efforts; and failed to use or analyze their own dispensing data to assist pharmacists in identifying prescriber-related red flags.
 - i. It is generally understood that the term “red flags” refers to a warning sign of danger. In the area of prescribing controlled substances, the term “red flags” has a similar meaning, and, in particular, a red flag is a warning sign that a particular prescription presents risk to the patient, a risk of diversion to unauthorized users, or both.
 - ii. In my own practice as an addiction medicine psychiatrist at Stanford for over 20 years, I have treated thousands of patients for addiction and dependence on prescription opioids, and the need for diligent investigation of red flags is an ever-present and recurring topic of discussion with the pharmacists who fill prescriptions for my patients, especially when controlled substances are prescribed.
 - iii. My relationship with pharmacists is collaborative, with the mutual goal of protecting the best interests of patients in receiving the proper medication, and the best interests of the community as a whole in preventing controlled substances from diversion to unauthorized users. Pharmacists regularly contact me to verify that I have prescribed the medication presented by the patient, or to inform me of any concerns they may have about the prescription. It is my practice to consult the PDMP, and it is my expectation that the pharmacist will also do so, to determine whether the patient has a pattern of early refills for controlled substances, has been on high doses or longer duration of controlled substances than medically indicated, has obtained multiple prescriptions from different prescribers for the same controlled drug or drug class (e.g., opioids), has obtained multiple prescriptions for controlled substances from multiple different pharmacies, has any contemporaneous or overlapping prescriptions that

could increase the risk of adverse events (e.g., an opioid and a benzodiazepine, which synergistically increase risk of respiratory depression and death), etc.

- iv. I am familiar with the Controlled Substance Act (CSA) and the regulations under the CSA assigning physicians the responsibility for proper prescribing for legitimate medical purposes, and the “corresponding responsibility” assigned to pharmacists.⁵⁰² These provisions formalize the *collaborative relationship*, described above, that should exist between doctors and pharmacists, for the protection of patients and the community from the dangers of controlled substances. I am aware, through my review of Industry documents and DEA enforcement decisions, that the CSA and its regulations have been interpreted as applicable to both *pharmacies* and *pharmacists*.
- An integral part of the pharmacists’ role entails the detection and investigation of red flags. These include perennial indicators that pertain across time periods, such as patients traveling unusual distances to get a prescription filled at a particular pharmacy; paying cash rather than using insurance; irregularities on the face of a prescription that may indicate forged or altered prescriptions; or patients’ behaviors that create suspicion of drug misuse and addiction. Other red flags may evolve over time, such as those relating to medical knowledge of the risks of co-prescribed medications, development of dose and duration limits, and new or changing patterns of drug use among those misusing or addicted to prescription drugs, e.g., drug “cocktails.”⁵⁰³
- vi. In a 2014 video called “Red Flags,” the National Association of Boards of Pharmacy stated that “by recognizing red flags to help establish the validity of a prescription, the pharmacist becomes the last line of defense in preventing misuse.”⁵⁰⁴ I agree with this statement. The presence of a red flag does not require automatic refusal to dispense, and there may be some

⁵⁰² Purpose of issue of prescription, 21 C.F.R. §1306.04.

“(a) A prescription for a controlled substance to be effective must be issued for a legitimate medical purpose by an individual practitioner acting in the usual course of his professional practice. The responsibility for the proper prescribing and dispensing of controlled substances is upon the prescribing practitioner, but a corresponding responsibility rests with the pharmacist who fills the prescription. An order purporting to be a prescription issued not in the usual course of professional treatment or in legitimate and authorized research is not a prescription within the meaning and intent of section 309 of the Act (21 U.S.C. 829) and the person knowingly filling such a purported prescription, as well as the person issuing it, shall be subject to the penalties provided for violations of the provisions of law relating to controlled substances.” 21 C.F.R. §1306.06 further provides, “Persons entitled to fill prescriptions. “A prescription for a controlled substance may only be filled by a pharmacist, acting in the usual course of his professional practice and either registered individually or employed in a registered pharmacy, a registered central fill pharmacy, or registered institutional practitioner.”

⁵⁰³ See, e.g., WMT_MDL_000524168

⁵⁰⁴ Complaint in *United States of America v. Walmart Inc. and Wal-Mart Stores Easy, LP*, Case No: 1:99-mc-09999 (D. Del. 2020) <https://www.justice.gov/opa/press-release/file/1347906/download>, p. 24, paragraph 86.

such warning signs that can be resolved. However, pharmacies are required to implement effective controls and procedures to guard against theft and diversion,⁵⁰⁵ and red flags cannot be detected or resolved if such controls or procedures do not exist, if they are not monitored, or if they are undermined or contradicted by actual practices.

- vii. Similarly, the former Deputy Assistant Administrator for DEA's Office of Diversion Control has stated, "When registrants at every level—practitioners, pharmacies and distributors—fail to fulfill their obligations," the CSA's "necessary checks and balances collapse... Because pharmacies are the entity providing the controlled substances to the end user, they are often the last major line of defense in the movement of legal pharmaceutical controlled substances from legitimate channels into the illicit market. It is, therefore, incumbent on pharmacies to ensure that controlled substances are only dispensed pursuant to valid prescriptions issued for legitimate medical purposes in the usual course of professional practice."⁵⁰⁶
- viii. It is clear that "Performance Metrics" based on fill quotas and wait times significantly influence pharmacy conduct and care. According to a survey by the National Association of Boards of Pharmacy, 83% of surveyed pharmacists believed that distractions due to performance metrics or measured wait times contributed to dispensing errors and that 49% felt specific time measurements were a significant contributing factor, which could reduce time for Drug Utilization Reviews (DURs) and ultimately result in unsafe conditions.⁵⁰⁷ These concerns are particularly acute with respect to controlled substances and the need to diligently investigate red flags through PDMPs, DURs, and other means. Pharmacy policies and procedures may purport to impose requirements of sound professional judgment, while establishing impressive lists of red flags and investigative methods, but these offer little protection when pharmacists are overwhelmed by the need to meet such performance metrics.
- ix. An article in a pharmacy professional journal stated: "Chain stores often require pharmacists to dispense 300 or more prescriptions a day, which translates to 37.5 prescriptions an hour in an 8-hour shift; that in turn translates to 1.6 minutes per prescription, during which time a pharmacist must verify the accuracy of the label, check the patient profile for duplications/interactions, contact prescribers if any issues arise, call the

⁵⁰⁵ See, Deposition of Demetra Ashley, In re: National Prescription Opiate Litigation (MDL No. 2804, Case No. 17-md-2804), March 11, 2021, at 104:15-107:19.

⁵⁰⁶ MNK-T1_0008415650 at 653. Declaration of Joseph Rannazzisi, submitted in *Holiday CVS, L.L.C., v. Holder*, Civ. No. 1:12-cv-191 (D.D.C Fed. 24, 2012).

⁵⁰⁷ National Association of Boards of Pharmacy. Performance Metrics and Quotas in the Practice of Pharmacy (Resolution 109-7-13), (June 5, 2013). <https://nabp.pharmacy/news/news-releases/performance-metrics-and-quotas-in-the-practice-of-pharmacy-resolution-109-7-13/>

insurer as needed, verify that the contents of the prescription vial are accurate, and counsel the patient on the medication - impossible!”⁵⁰⁸

Similarly, A University of Arizona College of Pharmacy study found that pharmacists’ workload threatened public safety, and that prescribing errors such as drug-drug interactions increased by 3% for every additional prescription filled per hour.⁵⁰⁹

- x. An investigation of prescribing practices conducted by the Chicago Tribune in 2016 found that 49% of chain pharmacies committed fundamental errors in dispensing prescriptions of two medications that were contraindicated for concurrent use, due to risks of severe and potentially fatal adverse effects, without warning customers of the dangers. The investigators tested 255 pharmacies and found, “CVS, the nation's largest pharmacy retailer by store count, had the highest failure rate of any chain in the Tribune tests, dispensing the medications with no warning 63 percent of the time. Walgreens, one of CVS' main competitors, had the lowest failure rate at 30 percent — but that's still missing nearly 1 in 3 interactions.”⁵¹⁰ Walmart pharmacies committed similar errors at a rate of 43 percent. While some pharmacists did properly warn, “in test after test, other pharmacists dispensed dangerous drug pairs at a fast-food pace, with little attention paid to customers. They failed to catch combinations that could trigger a stroke, result in kidney failure, deprive the body of oxygen or lead to unexpected pregnancy with a risk of birth defects.”⁵¹¹ The Tribune reporters said that their 2-year study “exposes fundamental flaws in the pharmacy industry. Safety laws are not being followed, computer alert systems designed to flag drug interactions either don't work or are ignored, and some pharmacies emphasize fast service over patient safety. Several chain pharmacists, in interviews, described assembly-line conditions in which staff hurried to fill hundreds of prescriptions a day.”
- xi. These failures to follow safety laws, and the emphasis on fast service over patient safety, are all the more important with controlled substances such as prescription opioids, due to their inherently addictive and potentially fatal consequences. Dispensing the combination of opioids and benzodiazepines, as Defendant Pharmacies did hundreds of thousands of times, carried particularly grave risks, and the sources referenced above support my opinion that such prescriptions were frequently issued without warnings of increased dangers.

⁵⁰⁸ Anna Leon Guerrero, *Pharmacy staffing levels can threaten patient lives*, Drug Topics (Nov. 4, 2015), <https://www.drugtopics.com/view/pharmacy-staffing-levels-can-threaten-patient-lives>.

⁵⁰⁹ Daniel C. Malone, *Pharmacists' Workload Contributes To Errors*, Science Daily (Apr. 24, 2007), <https://www.sciencedaily.com/releases/2007/04/070424130317.htm>.

⁵¹⁰ Sam Roe et al., *Pharmacies Miss Half of Dangerous Drug Combinations*, Chi. Tribune (Dec. 15, 2016), <https://www.chicagotribune.com/investigations/ct-drug-interactions-pharmacy-met-20161214-story.html>.

⁵¹¹ *Id.*

- xii. Significantly, the sources cited above were not exclusive to controlled substances, where the need for time to conduct diligent review is crucial to public health. Staggering numbers of prescription fills required by quotas and performance metrics are antithetical to the “sound professional judgment” that pharmacists must attempt to exercise under such conditions, making a mockery of the policies and procedures that impose such impossible standards.
- xiii. I have reviewed the policies and procedures of the Defendant Pharmacies in this case, as well as documents from the National Association of Chain Drug Stores (NACDS), medical literature relating to risks of prescription opioids and benzodiazepines (such as alprazolam, or Xanax) and muscle relaxants (such as carisoprodol, or Soma), and DEA decisions referencing those risks in the context of enforcing the CSA against pharmacies, including some of the Defendants’ pharmacies, and I have evaluated that information in light of my experience and expertise.
- xiv. Based on this evaluation, it is my opinion that the Pharmacy Defendants lacked policies and procedures to adequately investigate and resolve red flags of diversion and risk of medical complications during the first decade or more of the opioid epidemic; that even after certain policies and procedures were adopted, they were inadequate to meet the obligation to detect and resolve red flags before dispensing; that the Pharmacy Defendants could and should have analyzed their own data to assist pharmacists in identifying prescriber-related red flags⁵¹²; and that the Pharmacy Defendants implemented counter-productive measures, such as time pressures to fill prescriptions, financial incentives for rapid prescription fills, understaffing, permissive rather than mandatory use of PDMP resources, and failure to use their own data resources, which impaired pharmacists’ ability to carry out their responsibilities to investigate red flags. As further detailed below, the Pharmacy Defendants also failed to adequately respond to complaints from pharmacists who were concerned about pill mill prescribers and other abuses.
- xv. Because of the particular importance of the red flag for co-prescribing of opioids and benzodiazepines, particular attention to the evidence of increased risk is provided below. In short, the risk is two-fold. First, it has been known since at least 2002 that the addition of a benzodiazepine in a patient taking opioids increases the risk of respiratory depression, and this has accurately been described by an AMA speaker as a “potentially deadly combination.”⁵¹³ Second, it has been known since at least 2005 that prescription opioid patients seek benzodiazepines to accentuate the “high”

⁵¹² These include overprescribing, prescribing of higher dosages, prescribing patterns, and proportions of controlled substance/non-controlled prescribing.

⁵¹³ “Dr. Patrice Harris Talks About Opioids” The Augusta Chronicle, August 12, 2018
<https://www.youtube.com/watch?v=kbToYDmh16M>

of the opioid drug, thereby increasing the likelihood that either will be diverted for improper use.⁵¹⁴ Based on the Pharmacy Defendants' own documents, it is my opinion that they had an obligation to be aware of both the evolving medical literature and DEA enforcement actions, in determining the proper identification and resolution of red flags. In my opinion, as explained below, the Pharmacy Defendants failed to adequately identify or resolve a host of red flags, and, in particular, the dangerous co-prescribing of opioids and benzodiazepines.

- h. Medical literature has shown the increased risk of fatal respiratory depression by adding benzodiazepines to opioids since 2002.
 - i. In 2002, a peer-reviewed article analyzed mortality among patients taking the opioid methadone, and concluded: "*Benzodiazepines are more likely to contribute to fatal methadone toxicity in newly admitted maintenance patients and those taking methadone tablets for pain relief.*"⁵¹⁵
 - ii. In, 2007, a peer-reviewed article stated: "As central nervous system (CNS) depressants, benzodiazepines have been shown to act synergistically with opioids to reduce respiratory function, thereby increasing the risk of fatal and non-fatal overdose with opioids such as methadone and heroin."⁵¹⁶
 - iii. In 2012, a peer-reviewed investigation stated: "The co-abuse of BZDs and opioids is substantial and has negative consequences for general health, overdose lethality, and treatment outcome. Physicians should address this important and underappreciated problem with more cautious prescribing practices, and increased vigilance for abusive patterns of use. ...Although BZDs are a widely used practice for treatment of anxiety disorders, efforts must be taken to prevent the potentially lethal interaction that can occur when opioids and BZDs are administered simultaneously."⁵¹⁷
 - iv. In 2013, a Research Letter prepared by CDC officials stated, based on 2010 mortality data, "Opioids were frequently implicated in overdose deaths involving other pharmaceuticals. They were involved in the majority of deaths involving benzodiazepines (77.2%), antiepileptic and antiparkinsonism drugs (65.5%), antipsychotic and neuroleptic drugs (58.0%), antidepressants (57.6%), other analgesics, antipyretics, and antirheumatics (56.5%), and other psychotropic drugs (54.2%). Among

⁵¹⁴ *East Main Street Pharmacy*; Affirmance of Suspension Order, 75 Fed. Reg. 66,149, 66,163 (Oct. 27, 2010).

⁵¹⁵ Caplehorn, J. R., et al. Fatal methadone toxicity: signs and circumstances, and the role of benzodiazepines. *Aust N Z J Public Health*, 26(4), 358–363 (2002). <https://doi.org/10.1111/j.1467-842x.2002.tb00185.x>. (emphasis added).

⁵¹⁶ Nielsen, S., et al. Concurrent buprenorphine and benzodiazepines use and self-reported opioid toxicity in opioid substitution treatment. *Addiction* (Abingdon, England), 102(4), 616–622. (2007) <https://doi.org/10.1111/j.1360-0443.2006.01731.x>. (emphasis added).

⁵¹⁷ Jones, J. D., et al. Polydrug abuse: a review of opioid and benzodiazepine combination use. *Drug and Alcohol Depend.*, 125(1-2), 8–18. (2012) <https://doi.org/10.1016/j.drugalcdep.2012.07.004>., (emphasis added).

overdose deaths due to psychotherapeutic and central nervous system pharmaceuticals, the proportion involving only a single class of such drugs was highest for opioids (4903/16 651; 29.4%) and lowest for benzodiazepines (239/6497; 3.7%).”⁵¹⁸ This means that benzodiazepines alone are infrequently fatal, but frequently contribute to prescription opioid deaths.

- v. These sources show that the danger of co-prescribing opioids and benzodiazepines was known in the medical literature by 2002 and reaffirmed thereafter. A recent summary publication by the National Institute on Drug Abuse stated: “Every day, more than 136 Americans die after overdosing on opioids. However, *between 1996 and 2013, the number of adults who filled a benzodiazepine prescription increased by 67%, from 8.1 million to 13.5 million.* The quantity obtained also increased from 1.1 kg to 3.6 kg lorazepam-equivalents per 100,000 adults. Combining opioids and benzodiazepines can be unsafe because both types of drug sedate users and suppress breathing—the cause of overdose fatality—in addition to impairing cognitive functions. Unfortunately, many people are prescribed both drugs simultaneously. In a study of over 300,000 continuously insured patients receiving opioid prescriptions *between 2001 and 2013, the percentage of persons also prescribed benzodiazepines rose to 17 percent in 2013 from nine percent in 2001.* The study showed that people concurrently using both drugs are at higher risk of visiting the emergency department or being admitted to a hospital for a drug-related emergency. Previous studies have also highlighted the dangers of co-prescribing opioids and benzodiazepines. A cohort study in North Carolina found *that the overdose death rate among patients receiving both types of medications was 10 times higher than among those only receiving opioids.* In a study of overdose deaths in people prescribed opioids for noncancer pain in Canada, 60 percent also tested positive for benzodiazepines. *A study among U.S. veterans with an opioid prescription found that receiving a benzodiazepine prescription was associated with increased risk of drug overdose death in a dose-response fashion.*”⁵¹⁹
- vi. Co-prescribing of opioids and benzodiazepines has been a target of DEA enforcement of the CSA since at least 2005
- vii. As noted above, the co-prescription of benzodiazepines and opioids presents a significant risk of diversion due to the increased “high” compared to opioids alone, and this combination has been the subject of numerous DEA enforcement actions, including those summarized below. The Pharmacy Defendants’ own documents show their awareness of the

⁵¹⁸ Jones, et al., Pharmaceutical Overdose Deaths, United States, *JAMA* 2013;309(7):657-659. 2010. doi:10.1001/jama.2013.272

⁵¹⁹ National Institute on Drug Abuse. Benzodiazepines and Opioids, (Feb. 3, 2021). <https://www.drugabuse.gov/drug-topics/opioids/benzodiazepines-opioids>. (emphasis added)

need to be cognizant of DEA enforcement actions in devising effective controls against diversion.

■ In the *East Main Street Pharmacy* case, revocation of a Columbus, Ohio pharmacy's DEA Certificate of Registration was affirmed where the pharmacy filled "'large quantity prescriptions' for a benzodiazepine, two narcotic pain medications, and Soma, and '[t]hese drug combinations are generally known in the medical and pharmacy profession as being *avored by drug-seeking individuals*.'" ⁵²⁰ The prescriptions at issue were dispensed between September 2005 and February 2006. ⁵²¹ This decision also addresses the relationship between prescribing of "cocktails" and other red flags, as follows: "Respondent repeatedly dispensed drug cocktails for multiple controlled substances including oxycodone, hydrocodone, and alprazolam, as well as carisoprodol, a combination which is widely known in the pharmacy profession as being popular with drug abusers, and it did so in such quantities that any reasonable pharmacist would have asked how the prescriptions could possibly serve a legitimate medical purpose. The Government's Expert also explained that these cocktails would have a synergistic effect on a person's central nervous system and could cause respiratory depression. Accordingly, even if Volkman [the prescribing MD] told Mr. Fletcher [the pharmacist] that he did blood tests and MRIs, this would not make the prescriptions any more legitimate. *This alone supports the conclusion that Mr. Fletcher violated Federal law in dispensing the Volkman prescriptions.* 21 CFR 1306.04(a). The other evidence—such as that related to the quantities of the various drugs being prescribed, the dosing, and lack of individualization of therapy; the distances the patients were travelling and the typical method of payment; the fact that Mr. Fletcher knew that other pharmacists had refused to fill Volkman's prescriptions; the percentage and number of Volkman's prescriptions that were for controlled substances—is simply icing on the cake." ⁵²² Thus, the red flag of cocktail prescribing was sufficient to impose the duty of investigation before dispensing, regardless of the other listed red flags.

- ix. The *Holiday CVS* case involved a number of different red flags at a CVS pharmacy in Florida, where DEA agents had gone to pharmacies across the State to discuss drug diversion problems. The decision in the case included a statement that, "As an example of a red flag of diversion which would have been discussed during these DEA outreach programs, DI [DEA Investigator] Langston identified "a lot of prescriptions coming in for oxycodone, 30 milligrams (mg), oxycodone, 15 [mg]; Xanax

⁵²⁰ *East Main Street Pharmacy*; Affirmance of Suspension Order, 75 Fed. Reg. 66,149, (Oct. 27, 2010), at 66,149.

⁵²¹ *Id.* at 66,159.

⁵²² *Id.*, at pp. 66164-65. (emphasis added)

[alprazolam] two [mg].”⁵²³ “Indeed, in a December 2010 meeting, DEA Investigators explained to CVS officials various red flags to look for including the prescribing of the combination of oxycodone and alprazolam.”⁵²⁴ In the same case, the DEA’s expert testified, “Well, from a clinical pharmacist perspective that combination of drugs is what I would call a red flag because alprazolam and oxycodone are commonly diverted to nonmedical use.”⁵²⁵

- In the *Pharmacy Doctors Enterprises d/b/a Zion Clinic Pharmacy* DEA action, one of the red flag subjects of enforcement was described as follows: “The Show Cause Order alleged that Respondent filled opiate (hydromorphone) and benzodiazepine (alprazolam, clonazepam, diazepam, or lorazepam) prescriptions, a ‘common ‘drug cocktail’ popular with drug abusers,’ for the same customer on the same day at about the same time without first having resolved the red flags of diversion. The Show Cause Order cited 14 prescriptions, or seven pairs of ‘drug cocktail’ prescriptions, that Respondent allegedly filled during the period of October 2012 through January 2013.”⁵²⁶ The court stated, regarding the DEA’s expert: “Dr. Gordon addressed whether a muscle relaxant had to be present to constitute a drug cocktail. She stated that, ‘Cocktail medications usually . . . are a combination of an opioid plus or minus a benzo plus or minus a muscle relaxant’ ... Then she explained: ‘But what I’ve seen . . . lately is the doctors have stopped the Soma, and they are just doing, now, high doses of Dilaudid, high doses of benzos. It used to be Oxys. Now they’ve switched to hydromorphone. So you see . . . the flags change.’ She added that, ‘I see the physicians and drug diverters trying to eliminate one of the components of the cocktail to try to get away with diverted drugs.’”⁵²⁷ The Court concluded: “Based on all of the evidence in the record, I find that Respondent filled prescriptions without having resolved the red flags of customers presenting prescriptions with a combination of an opiate and a benzodiazepine which is a common ‘drug cocktail’ popular with drug abusers.”⁵²⁸

- xi. In light of the materials summarized above, it is my opinion that a red flag for the combination of opioids and benzodiazepines should have been in place by no later than 2007, based on the medical literature, and by no later than 2010, based on DEA enforcement actions. Despite these red

⁵²³ *Holiday CVS, L.L.C., d/b/a CVS/Pharmacy*, Nos. 219 and 5195; Decision and Order, 77 Fed. Reg. 62,316. (Oct. 12, 2012), at 62,325; <https://www.govinfo.gov/content/pkg/FR-2012-10-12/pdf/2012-25047.pdf>, . (emphasis added)

⁵²⁴ *Id.*, at 62,334.

⁵²⁵ *Id.*, at 62,333.

⁵²⁶ *Pharmacy Doctors Enterprises d/b/a Zion Clinic Pharmacy*; Decision and Order, 83 Fed. Reg. 10,876 (Mar. 13, 2018), at 10,877 <https://www.federalregister.gov/documents/2018/03/13/2018-05020/pharmacy-doctors-enterprises-dba-zion-clinic-pharmacy-decision-and-order>, (emphasis added).

⁵²⁷ *Id.*, at p. 10,888.

⁵²⁸ *Id.*, at p. 10,889-90.

flags, the Pharmacy Defendants dispensed prescriptions for an opioid and a benzodiazepine thousands of times in Lake and Trumbull counties. In light of the known risks to health, and the attraction of drug seekers to this combination, this is strong evidence of the lack of effective controls against diversion, and a likely contributor to adverse health effects in the affected communities.

- xii. The *East Main Street* case, which involved combinations that also included a muscle relaxant, would support a red flag for that combination as of the 2005-06 prescriptions that were the target of DEA enforcement.
 - xiii. The sections that follow provide summaries of the evolution of the Pharmacy Defendants' policies and procedures, and the deficiencies described above.
- i. Pharmacy Defendant Walmart lacked effective controls and actively undermined efforts of pharmacists to prevent diversion.
 - i. By 2005, the prescription opioid epidemic was several years into its evolution, having begun in the mid-to-late 1990s. As recounted previously in this Report, the medical literature, CDC data, and articles in the lay press had made clear that prescription opioids were the cause of a significant spike in overdose and mortality.⁵²⁹ The DEA had already begun enforcement actions against pharmacies for failure to investigate or resolve red flags of diversion and increased risk of drug cocktails in 2005.⁵³⁰ The need for effective controls against diversion had existed since the passage of the CSA, decades earlier, but that need was magnified by the prescription opioid epidemic in the early 2000s.
 - ii. In November 2005, Walmart adopted Section 1703 of its Pharmacy Operations Manual (POM) which included instructions for handling suspected forged or altered prescriptions, such as contacting the prescribing physician for verification, and contacting local authorities as recommended by the DEA. This POM provision did not mention concerns over diversion or risks to customers from drug combinations or "cocktails," did not address prescriber characteristics such as high doses or frequent prescribing, and did not provide information about indicators of suspected diversion or prescribing outside the scope of legitimate medical purpose.⁵³¹ As such, the 2005 version of Section 1703 was inadequate to the task of instructing pharmacists on detection and resolving red flags before dispensing prescription opioids.

⁵²⁹ See Section §C.3 of this Report.

⁵³⁰ *East Main Street Pharmacy*; Affirmance of Suspension Order, 75 Fed. Reg. 66,149, (Oct. 27, 2010). (Which described misconduct in 2005-2006 as the basis for DEA enforcement.)

⁵³¹ WMT_MDL_000069188

- Information about the severity of the epidemic and the risks of opioids continued to become widely known. On May 10, 2007, the New York Times reported that Purdue and three current and former executives “pleaded guilty today in federal court here to criminal charges that they misled regulators, doctors and patients about the drug’s risk of addiction and its potential to be abused.”⁵³² This widely publicized event gave further notice to Pharmacy Defendants, and to the world at large, that OxyContin, a very popular and profitable drug, carried major risks of abuse, and that the risks had been downplayed.
- iv. In August 2007, three months after the news of Purdue’s guilty plea, Walmart issued an update to Section 1703 of the POM, which added a section entitled, “Potential Indicators of Fraudulent, Forged or Altered Prescriptions.” This section advised to “Watch for unusually high quantities and/or dosages,” customers unwilling to bill to their insurance, and indicators of fraud on the face of the prescription, such as different colors of ink or different handwriting. The 2007 POM did not mention concerns over patients traveling long distances, high volume prescribers (pill mills), diversion or risks to customers from drug combinations or “cocktails,”⁵³³ although DEA had begun enforcement actions prior to that time on the basis of pharmacies dispensing in spite of such concerns.
 - v. The April 2009 version of POM 1703 included the introductory statement, “This policy provides guidance on how to identify and handle forged or altered prescriptions in order to comply with State and Federal requirements, detect and prevent diversion, protect the safety of our associates and patients, and ensure that reasonable grounds exist to refer forged and/or altered prescriptions to law enforcement.”⁵³⁴ The POM then listed factors suggested by the DEA that may be “indicators of forged or altered prescriptions,” including, “Unusually high quantities and/or dosages that differ from usual medical use,” and “Multiple patients appearing in a short period of time bearing similar prescriptions from the same physician.”⁵³⁵
 - vi. This POM reference to “unusually high quantities” and “multiple prescriptions from the same physician” appears to relate to the pill mill problem. However, this belated measure did not correct Walmart’s actual practice. As documented in the December 2020 Complaint of the Department of Justice (DOJ), Walmart ignored repeated pleas from its pharmacists to refuse to fill opioid prescriptions from known pill mills. In fact, over the course of 44 pages, the Complaint provides details of “20

⁵³² Meier, B., “In Guilty Plea, Oxycontin Maker to Pay \$600 Million.” New York Times (May 10, 2007). <https://www.nytimes.com/2007/05/10/business/11drug-web.html>.

⁵³³ WMT_MDL_000069223

⁵³⁴ WMT_MDL_000069228

⁵³⁵ *Id.*

examples of the numerous prescribers whose *egregious and unprofessional prescribing practices were known to Walmart*. The examples are organized in alphabetical order by the prescribers' initials. In each example, Walmart pharmacists repeatedly recognized, and reported to Walmart's compliance unit, that a particular prescriber was issuing prescriptions without a legitimate medical purpose or outside the usual course of professional practice. In each example, *Walmart's compliance unit knew that its pharmacists were continuing to be presented with prescriptions issued by those prescribers, and that, based on the reported red flags, there was a very high probability that the prescribers were regularly issuing invalid controlled-substance prescriptions.*⁵³⁶ These examples included a Florida physician whose "patients" filled his prescriptions at Walmart stores in 32 states around the country, including Ohio, as well as dispensing violations at Walmart stores in Arkansas, Colorado, Delaware, Georgia, Indiana, North Carolina, Pennsylvania, Texas, and Wisconsin.⁵³⁷ In short, there were nationwide CSA violations throughout Walmart's system.

- vii. In February 2009, Walmart POM 1311, to which POM 1703 referred, stated Walmart's "uniform national policy" to determine whether a proper prescriber-patient relationship exists, and provided a list of indicators, including prescribers outside the US or out-of-state; prescriptions outside the scope of customary practice; prescribers known to be retired or deceased; "the prescription is for a large quantity (especially controlled substances)," and "the prescription is for a large number of a particular strength."⁵³⁸ A similar list appeared in the March 2011 version of POM 1311.⁵³⁹
- viii. While the POM 1703 and 1311 provisions of 2009 and 2011 cite DEA guidance as their source, those provisions omit numerous red flags of potentially illegitimate prescribing that had been the subject of prior DEA enforcement actions, which went well beyond the scope of "forged or altered prescriptions," including traveling significant distances from one's residence to a pharmacy; paying in cash; and drug combinations, or "cocktails," consisting of either an opioid (such as oxycodone) plus a benzodiazepine (such as alprazolam), or a "trinity consisting of those two drug categories with the addition of a muscle relaxant (such as carisoprodol). These red flags were identified in the *East Main Street* case,

⁵³⁶ Complaint in *United States of America v. Walmart Inc. and Wal-Mart Stores Easy, LP*, Case No: 1:99-mc-09999 (D. Del. 2020). Available at <https://www.justice.gov/opa/press-release/file/1347906/download>, p. 50-94, paragraphs 176-356 (emphasis added).

⁵³⁷ *Id.*, at paragraph 302.

⁵³⁸ WMT_MDL_000069108 at 69109.

⁵³⁹ WMT_IN_AG_00000066 at 00000067.

which was filed in April 2009, based on conduct that had occurred in 2005-2006, and decided in 2010 in a published order.⁵⁴⁰

- ix. The absence of red flags for opioids + benzodiazepines, and for the trinity of those two drugs plus a muscle relaxant, is a significant omission that failed to properly instruct Walmart's pharmacists as to both the potential for diversion, since the drugs were known to increase the high among drug users, and the increased risks of medical complications, especially the synergistic effects on respiratory depression, which were known to increase the risk of overdose and death well before 2009.⁵⁴¹
- Despite the acknowledgment of large prescribed quantities of opioids as warning signs in the 2009 and 2011 versions of POM 1311, Walmart's actions did not match the policy. Instead, "During the Dispensing Violations Period, from June 26, 2013, to the present,⁵⁴² *Walmart violated the CSA's dispensing rules on a sweeping national scale, filling enormous numbers of invalid controlled-substance prescriptions.*"⁵⁴³
- In light of the materials summarized above, it is my opinion that a red flag for the combination of opioids and benzodiazepines should have been in place by no later than 2007, based on the medical literature, and by no later than 2010, based on DEA enforcement actions. The East Main Street case, which involved combinations that also included a muscle relaxant, would support a red flag for that combination as of the 2005-06 prescriptions that were the target of DEA enforcement. In light of the known risks to health, and the attraction of drug seekers to this combination, this large number of prescriptions is strong evidence of the lack of effective controls against diversion, and a likely contributor to adverse health effects in the affected communities.⁵⁴⁴
- xii. Following an enforcement proceeding where DEA accused Walmart of violating its dispensing violations, in March 2011, "DEA and Walmart entered into a nationwide memorandum of agreement ("MOA") to resolve an administrative action predicated upon a California Walmart pharmacy's alleged failure to comply with its dispensing obligations when filling controlled substance prescriptions, including filling such prescriptions where the prescription was not issued for a legitimate medical purpose or

⁵⁴⁰ East Main Street Pharmacy; Affirmance of Suspension Order, 75 Fed. Reg. 66,149 (Oct. 27, 2010).

⁵⁴¹ See summary of opioid + benzodiazepine medical literature, above, at Section §C.6.h. See, e.g., Jones, et al., Polydrug abuse: A review of opioid and benzodiazepine combination use. *Drug Alcohol Depend.* 2012 September 1; 125(1-2): 8–18. doi:10.1016/j.drugalcdep.2012.07.004.

⁵⁴² The "present" would mean December 20, 2020, when the Complaint was filed.

⁵⁴³ Complaint in *United States of America v. Walmart Inc. and Wal-Mart Stores Easy, LP*, Case No: 1:99-mc-09999 (D. Del. 2020). Available at <https://www.justice.gov/opa/press-release/file/1347906/download>, p.29, paragraph 105. (emphasis added.)

⁵⁴⁴ *Id.*, at 68642.

by a prescriber acting within the usual course of professional practice. The MOA was in effect from March 2011 through March 2015. In the MOA, Walmart committed to, among other things, ‘maintain a compliance program, updated as necessary, designed to detect and prevent diversion of controlled substances as required by the Controlled Substances Act.’”⁵⁴⁵

- xiii. While the MOA demonstrates Walmart’s explicit knowledge of the problem of opioid diversion, the MOA did not result in Walmart’s compliance with the CSA; instead, prescriptions from pill mill doctors continued: “Even when pharmacists determined by themselves that prescribers were acting as pill mills, Walmart’s compliance unit refused to let the pharmacists categorically refuse to fill all prescriptions issued by such prescribers. Rather, the compliance unit told pharmacists that they needed to consider each individual prescription—an approach that made it impractical for pharmacists to reject all prescriptions issued by these pill-mill prescribers, particularly given the strict time pressures Walmart imposed on its pharmacists for filling prescriptions.”⁵⁴⁶ The “enormous” CSA violations were ongoing, as documented in the DOJ Complaint. In 2012, Walmart adopted a policy *requiring* that its pharmacists conduct a PDMP check for every request to dispense oxycodone immediate release 30 mg, because it had been identified “through careful analysis as a highly prescribed medication with high abuse potential.”⁵⁴⁷ This requirement eventually was incorporated into Walmart’s POM 1316, in April 2016.⁵⁴⁸ In my opinion, Walmart could have and should have required that its pharmacists conduct a PDMP check for *all* opioids, not just oxycodone 30 mg, and that requirement should have been stated consistently in its POMs.
- xiv. On January 10, 2013, the NACDS convened a meeting of the “DEA Compliance Working Group,” which included a Walgreens representative as Co-Chair, and representatives of CVS, Rite-Aid and Walmart as “Participants.”⁵⁴⁹ In advance of the meeting, NACDS circulated a legal overview of considerations for development and implementation of a voluntary, “industry-wide code for controlled substance dispensing;” an overview of DEA standards and red flags from recent DEA cases; and a summary of medical literature relevant to red flags for prescription drug abuse.⁵⁵⁰ Significantly, NACDS cited “the need to be forward-thinking with the code, and go beyond simply codifying known ‘red flags’ for

⁵⁴⁵ Complaint in *United States of America v. Walmart Inc. and Wal-Mart Stores Easy, LP*, Case No: 1:99-mc-09999 (D. Del. 2020). Available at <https://www.justice.gov/opa/press-release/file/1347906/download> ., p.40-41, paragraphs 136-137.

⁵⁴⁶ *Id.*, at p. 48, paragraph 166.

⁵⁴⁷ WMT_MDL_000069746.

⁵⁴⁸ WMT_MDL_000043015

⁵⁴⁹ WAGMDL00496404; WAGMDL00496402

⁵⁵⁰ WAGMDL00496404.

abuse.”⁵⁵¹ This statement, in a document that included input from all of the major chain pharmacies, shows that by 2013 an adequate system was not in place to prevent against misuse and diversion, and a better top-down system was needed across all stores.

- A summary of the January 10, 2013 meeting, circulated to participants, stated that “Key elements” to be included in the code would be, “ensuring an appropriate prescriber-patient relationship, ensuring physicians have a relevant scope of practice for the prescribed medication, and focus of commonly abused cocktails.”⁵⁵²
- xvi. The January 2013 NACDS summary provided a table of red flags, broken into the categories of Patient Conduct, Physician Conduct, and Pharmacy/pharmacist Conduct.⁵⁵³
 - A. The “Patient Conduct” category included traveling significant distance to fill a prescription, paying in cash, behaviors consistent with being under the influence of controlled substances, and “doctor shopping.” As to the latter, the NACDS proposed recommendations included, “Require the review of PDMP prior to dispensing all high-risk medication.”⁵⁵⁴
 - B. The “Physician Conduct” category included large numbers or percentages of controlled substance prescriptions; prescribing “high-alert drugs,” including opioids, benzodiazepines and barbiturates; and prescribing “questionable ‘cocktails’ of highly diverted drugs,” mentioning as examples, (a) oxycontin, an opioid + alprazolam, a benzodiazepine, and (b) the trinity of an opioid, a benzodiazepine, and a muscle relaxant. As to the “cocktails” red flag, the NACDS summary cited the *Holiday* and *East Main* DEA decisions, and the “Potential Action” included, “Leverage drug screening software to help identify cocktails through unique alert.”⁵⁵⁵
 - C. The Pharmacy/pharmacist Conduct” category included “Excessive volume and rate of growth of controlled substances,” and the NACDS Potential Actions included a mandatory 48-72 hour period for enhanced scrutiny of prescriptions for high-risk substances;

⁵⁵¹ *Id.*

⁵⁵² *Id.*, at 6405.

⁵⁵³ WAGMDL00496407.

⁵⁵⁴ *Id.*, at 6409.

⁵⁵⁵ *Id.*, at 6410-6415.

removing controlled substances from dispensing incentive programs; or ceasing to carry high-risk products for dispensing.⁵⁵⁶

- xvii. On January 25, 2013, Walmart replied to NACDS' list of proposed red flags and suggested responses by the pharmacy and pharmacists. Walmart disagreed with many of the NACDS proposals, including identifying a red flag for "Excessive volume and rate of growth of dispensing controlled substances."⁵⁵⁷ This is a telling disagreement, in light of the misconduct described in the DOJ Complaint, highlighting Walmart's history of filling "enormous" quantities of controlled substance prescriptions, which would necessarily have contributed to "excessive volume and rate of growth" of such dispensing. Walmart's own data on prescription opioid sales, mandated to be kept by the CSA,⁵⁵⁸ would have provided Walmart with the data to analyze this red flag, which it could and should have done, but did not do.
- xviii. As to NACDS' proposed action of removing controlled substances from dispensing incentive programs, Walmart's response stated, "Incentive programs should be entirely agnostic as to the type of prescriptions (controlled substances or non-controlled drugs) filled."⁵⁵⁹ In other words, Walmart's position *included controlled substances in programs that incentivized their sale*. This policy inappropriately encouraged the sale of addictive drugs, and made it more likely that consumers would be exposed to their dangers. In particular, an incentivized dispensing program rewards speed and efficiency, which may be appropriate for low-risk drugs, but those values are contrary to the vigilance and diligent investigation required as to prescriptions for controlled substances, especially during an epidemic of diversion and overdose mortality. The DOJ Complaint documents the pattern of inappropriate time pressures to fill prescriptions rapidly, and the concerns of pharmacists that speed did not allow for diligent investigation.⁵⁶⁰
- xix. Walmart's Pharmacy Facility Incentive Plan for 2012 provided for bonus payments based on numbers of prescriptions, amount of profits, and customer relations, compared to established benchmarks. The program was designed "to reward our associates if pre-defined business goals are

⁵⁵⁶ *Id.*, at 6415.

⁵⁵⁷ WMT_MDL_000891159 at 1175-1176.

⁵⁵⁸ Deposition of Demetra Ashley, In re: National Prescription Opiate Litigation (MDL No. 2804, Case No. 17-md-2804), March 11, 2021, 132:14-134:17.

⁵⁵⁹ WMT_MDL_000891159, at 1175.

⁵⁶⁰ See Complaint in *United States of America v. Walmart Inc. and Wal-Mart Stores Easy, LP*, Case No: 1:99-mc-09999 (D. Del. 2020). Available at <https://www.justice.gov/opa/press-release/file/1347906/download>. at p. 6, paragraph 6: "Walmart made it difficult for its pharmacists to follow the rules. Walmart managers put enormous pressure on pharmacists to fill prescriptions—requiring pharmacists to process a high volume of prescriptions as fast as possible, while at the same time denying them the authority to categorically refuse to fill prescriptions issued by prescribers the pharmacists knew were continually issuing invalid prescriptions."

met or exceeded.”⁵⁶¹ As numbers of scripts went up, and as profits went up, incentive payments increased. A Management Incentive Plan (MIP) bonus provided for additional payments to all eligible associates based on the extent to which the number of annual prescriptions exceeded 190,000.⁵⁶² The Incentive Plan made no mention of patient safety goals, nor red flag detection goals. For as long as such programs were in place, they contradicted the need for effective controls against diversion, instead emphasizing speed and profits.

- xx. As to the mandatory use of the PDMP included in the NACDS red flag document, Walmart responded, “If the pharmacist has reason to believe that the prescription has not been issued for a legitimate medical purpose, tools such as PDMP should be utilized.”⁵⁶³ Walmart’s response regarding the PDMP mirrored its POM 1316, which pertained to use of Prescription Monitoring Programs, or PMPs. The March 2011 and August 2012 versions of POM 1316 advised Walmart pharmacists that the use of a PDMP was permissive, not mandatory, and would only be used if the pharmacist believed, in the exercise of professional judgment, that the use of the PDMP would be helpful in determining whether a prescription was legitimate.⁵⁶⁴ But the use of the PDMP is to assist in making the determination of legitimacy in the first place. Particularly in the face of an ongoing epidemic of prescription opioid overdose mortality, the mandatory use of the PDMP would have provided essential information to prevent excessive prescribing of opioids alone, and of opioid cocktails with other drugs that increase likelihood of diversion and severe medical complications.
- xxi. On August 7, 2013, an internal Walmart email from C. Scott Ortolani, RPh and Walmart Market Director, to Brad Nelson, stated the “inspectors collectively feel Walmart is [s]tarting to become a ‘funnel’ with C-II’s due to more liberal policies on dispensing pain meds.”⁵⁶⁵ This is consistent with, and supportive of, the facts alleged in the DOJ complaint of December 2020.
- xxii. Based on my review of Walmart’s chronology of POMs, a red flag for “cocktails” of “commonly abused drugs” or drug combinations that could cause “medical complications” ultimately appeared in the July 2015

⁵⁶¹ WMT_MDL_000043526, at 43528.

⁵⁶² *Id.*, at 43528-535.

⁵⁶³ WMT_MDL_000891159 at 1177.

⁵⁶⁴ WMT_MDL_000069142; WMT_MDL_000069148. (Note that Walmart’s term, “PMP,” has the same meaning as the term “Prescription Drug Monitoring Program,” or PDMP, as used by the NACDS and elsewhere.)

⁵⁶⁵ WMT_MDL_000649191

version of POM 1311.⁵⁶⁶ The inclusion of this provision in 2015 supports my opinion that Walmart believed it was proper to instruct its pharmacists to be aware of the risks of diversion and medical complications presented by drug cocktails, and my further opinion that it was improper to omit those red flag instructions to pharmacists for a period of years prior to July 2015.

- xxiii. Despite the lack of a comprehensive list of red flags in the Walmart POMs, it appears from the DOJ Complaint that at least some Walmart pharmacists were aware of the red flags for “cocktail” prescribing, and that they brought those concerns to their supervisors, yet Walmart continued to fill such prescriptions without regard for obvious risks of diversion and serious medical complications or death. For example, according to the DOJ Complaint, “[f]rom June 26, 2013, through January 2017, despite Walmart’s knowledge of red flags indicating a very high probability that [physician] F.B. regularly issued invalid prescriptions for controlled substances, Walmart filled more than 500 controlled-substance prescriptions written by F.B. for Medicare patients.” Over 200 of those prescriptions were for Schedule II controlled substances, including “cocktails” of Percocet [opioid plus acetaminophen], Xanax [benzodiazepine], Adderall (stimulant) and sometimes Soma [muscle relaxant].⁵⁶⁷
- xxiv. On August 31, 2016, the FDA determined that the risk of benzodiazepines in combination with opioids was sufficient to warrant addition of a Boxed warning, in response to a Citizen’s Petition requesting such action. The Petition itself was based on medical literature from prior years.⁵⁶⁸ The FDA’s response to the Petition cited literature published between 1999 and 2014 in support of the statement that “in certain circumstances, either opioids or benzodiazepines independently can depress respiration. When combined, these drugs can cause greater respiratory depression than either

⁵⁶⁶ WMT_IN_AG_00000079 at 00080. (Note that the first page of the document states a date of “June 2105,” while the remaining pages all state “July 2015.”)

⁵⁶⁷ Complaint in *United States of America v. Walmart Inc. and Wal-Mart Stores Easy, LP*, Case No: 1:99-mc-09999 (D. Del. 2020). Available at <https://www.justice.gov/opa/press-release/file/1347906/download>, p. 55, paragraphs 190-191.

⁵⁶⁸ See U.S. Food & Drug Administration, *New Safety Measures Announced for Opioid Analgesics, Prescription Opioid Cough Products, and Benzodiazepines*, (August 31, 2016). Available at <https://www.fda.gov/drugs/information-drug-class/new-safety-measures-announced-opioid-analgesics-prescription-opioid-cough-products-and> : “After an extensive review of the latest scientific evidence, the U.S. Food and Drug Administration announced today that it is requiring class-wide changes to drug labeling, including patient information, to help inform health care providers and patients of the serious risks associated with the combined use of certain opioid medications and a class of central nervous system (CNS) depressant drugs called benzodiazepines. Among the changes, the FDA is requiring boxed warnings and patient-focused Medication Guides for prescription opioid analgesics, opioid-containing cough products, and benzodiazepines – nearly 400 products in total – with information about the serious risks associated with using these medications at the same time. Risks include extreme sleepiness, respiratory depression, coma and death.”

drug would by itself, as can other CNS depressant drugs when combined with opioids. For this reason, the labeling of many opioid analgesics and benzodiazepine drugs currently contains warnings about the risks of concomitant use of opioid analgesics and benzodiazepines. To date, however, these warnings have not been presented in a boxed warning.”⁵⁶⁹ The FDA’s action was explicitly based on past literature that documented the risk of this combination.

- xxv. The December 2016 and January 2017 versions of Walmart POM 1311 included text as to red flags for “cocktails” that was identical to the provisions of the July 2015 version of POM 1311.⁵⁷⁰ However, beginning in February 2017, the red flag for “cocktails” added the qualifier, “(i.e. an opioid, a benzodiazepine, and a muscle relaxant). This is often referred to as the ‘trinity’ or ‘holy trinity.’”⁵⁷¹ This change was ill-advised, since it specified to the pharmacist that the only cocktail to be concerned about must have included all three drugs. That is contrary to the medical literature, which identifies opioids + benzodiazepines as a high-risk combination, and also to DEA precedent, which identified the risks of both diversion and medical complications in earlier decisions as to the opioids + benzodiazepines combination, regardless of the presence of any other drug. The June 2017 version of POM 1311 lists the same set of red flags that listed the “trinity” of opioids + benzodiazepines + muscle relaxant, but did not identify opioids + benzodiazepines (without the third drug), as a red flag.⁵⁷²
- xxvi. Under the circumstance of Walmart’s egregious disregard for red flags of all kinds, including prescription of known “cocktails” that increase the high while also increasing the likelihood of overdose mortality, the question of whether the written policy included a red flag only for the “trinity” may seem to be of relatively minor importance. However, given that Walmart has more than 5,000 pharmacies that dispense prescription opioids and other controlled substances, and that each pharmacy employs multiple pharmacists, all of whom were required to be familiar with the POM and its provisions, accurate and appropriate POM policies to identify red flags would have informed all pharmacists of the need to investigate prescriptions for opioids in combination with benzodiazepines that were

⁵⁶⁹ See Letter from Janet Woodcock to Leana Wen M.D. and Nicole Alexander-Scott M.D., RE: Docket No. FDA-2016-P-0689, U.S. Food & Drug Administration, Center for Drug Evaluation and Research, Available at https://downloads.regulations.gov/FDA-2016-P-0689-0003/attachment_1.pdf, at p. 4, citing Jann M, Kennedy WK, Lopez G. Benzodiazepines: a major component in unintentional prescription drug overdoses with opioid analgesics. *J Pharm Pract.* 2014;27(1):5-16; Pattinson KT. Opioids and the control of respiration. *Br J Anaesth* (2008) Jun;100(6):747-58; Gueye PN, Borron SW, Risede P, et al. Buprenorphine and midazolam act in combination to depress respiration in rats. *Toxicol Sci* (2002);65:107-14; White JM, Irvine RJ. Mechanisms of fatal opioid overdose. *Addiction* (1999) 94(7), 961-972.

⁵⁷⁰ WMT_IN_AG_00000084 at 0085.

⁵⁷¹ WMT_IN_AG_00000118 at 0119.

⁵⁷² WMT_NH_AG_00000124

dispensed at Walmart stores. Those prescriptions should have been subjected to a red flag investigation to determine whether they were issued for a legitimate medical purpose or posed a risk of diversion. It is reasonable to conclude that a substantial number of such prescriptions were illegitimate, in light of the known facts of drug-seeking use of that combination.

- xxvii. As part of my work in this case, I have reviewed substantial investigative reporting, including interviews with Walmart pharmacists, that reinforces the allegations of the DOJ 2020 Complaint, including a lengthy article published by Pro Publica on March 25, 2020, which summarized the key findings of a DOJ investigation as follows: “Opioids dispensed by Walmart pharmacies in Texas had killed customers who had overdosed. The pharmacists who dispensed those opioids had told the company they didn’t want to fill the prescriptions because they were coming from doctors who were running pill mills. They pleaded for help and guidance from Walmart’s corporate office. Investigators had obtained records of similar cries for help from Walmart pharmacists all over the country: from Maine, North Carolina, Kansas and Washington, and other states. They reported hundreds of thousands of suspicious or inappropriate opioid prescriptions. One Walmart employee warned about a Florida doctor who had a list of patients from Kentucky that have been visiting pharmacies in all of central Wisconsin recently.’ That doctor had sent patients to Walmarts in more than 30 other states. In response to these alarms, Walmart compliance officials did not take corporate-wide action to halt the flow of opioids. Instead, they repeatedly admonished pharmacists that they could not cut off any doctor entirely. They could only evaluate each prescription on an individual basis. And they went further. An opioid compliance manager told an executive in an email, gathered during the inquiry and viewed by ProPublica, that Walmart’s focus should be on ‘driving sales.’”⁵⁷³
- xxviii. Similarly, a recent NPR investigation stated, “Walmart pharmacists warned for years about opioid sales that appeared dangerous or illegal” and that pharmacists faced “intense pressure to sell opioids and fill prescriptions quickly and without asking a lot of questions.”⁵⁷⁴
- xxix. In addition to the dispensing violations of the CSA summarized above, the DOJ Complaint alleges that, as the operator of its own distribution centers, which ceased distributing controlled substances in 2018, Walmart received

⁵⁷³ Eisinger J., Bandler J. “Walmart Was Almost Charged Criminally Over Opioids. Trump Appointees Killed the Indictment.” ProPublica (March 25, 2020). Available at <https://www.propublica.org/article/walmart-was-almost-charged-criminally-over-opioids-trump-appointees-killed-the-indictment>.

⁵⁷⁴ Mann, B., "Former Walmart Pharmacists Say Company Ignored Red Flags As Opioid Sales Boomed." NPR (January 3, 2017). Available at <https://www.npr.org/2021/01/03/950870632/former-walmart-pharmacists-say-company-ignored-red-flags-as-opioid-sales-boomed>

hundreds of thousands of suspicious orders that it failed to report as required to by the DEA. The dispensing and distribution violations “helped to fuel the prescription opioid crisis.”⁵⁷⁵ A DOJ press release further cited an example of a physician prosecuted by the DOJ and convicted of illegal opioid distribution, who had specifically directed his patients to have their prescriptions filled at Walmart, adding that “Walmart’s own pharmacists reported concerns about the doctor up the corporate chain, but for years, Walmart did nothing—except continue to dispense thousands of opioid pills.”⁵⁷⁶

- xxx. Importantly, the DOJ Complaint states that “WALMART, AS A PHARMACY, VIOLATED THE CSA,”⁵⁷⁷ rather than assigning blame to the individual pharmacists. I agree that the extent of CSA violations described in the DOJ Complaint cannot be attributed to individual pharmacists, but instead the responsibility must be attributed to the corporation itself. This is particularly true in light of the documented complaints from individual Walmart pharmacists to their supervisors asking for support in detecting and acting on red flags, which did not result in corporate support and hence unlawful dispensing continued.
- xxxi. I am aware that Walmart filed a lawsuit against the DOJ and the DEA in October 2020, claiming that the company was constrained to fill doctors’ prescriptions, and that the DEA continued to allow those physicians to practice and prescribe.⁵⁷⁸ I am also aware that a federal judge dismissed Walmart’s lawsuit, and that Walmart plans to appeal.⁵⁷⁹
- xxxii. In my opinion, Walmart, and other pharmacies, had an important role to play in preventing the distribution of opioids that fueled the epidemic, regardless of the actions of individual prescribers, government agencies, or the outcome of the litigation between Walmart and the DOJ. Walmart’s conduct, as described in the DOJ Complaint and news reports cited above, appears to be the result of careful investigation, and such conduct significantly contributed to the opioid epidemic.

⁵⁷⁵ Press Release, *Department of Justice Files Nationwide Lawsuit Against Walmart Inc. for Controlled Substances Act Violations*, Department of Justice (December 22, 2020). Available at <https://www.justice.gov/opa/pr/departments-justice-files-nationwide-lawsuit-against-walmart-inc-controlled-substances-act>

⁵⁷⁶ *Id.*

⁵⁷⁷ Complaint in *United States of America v. Walmart Inc. and Wal-Mart Stores Easy, LP*, Case No: 1:99-mc-09999 (D. Del. 2020). Available at <https://www.justice.gov/opa/press-release/file/1347906/download>, at p. 29. (all caps in original.)

⁵⁷⁸ Press Release, *Walmart Sues DOJ and DEA Seeking Clarity for Pharmacists in Dispensing Prescription Opioids*, Walmart (Oct. 22, 2020). Available at <https://corporate.walmart.com/newsroom/2020/10/22/walmart-sues-doj-and-dea-seeking-clarity-for-pharmacists-in-dispensing-prescription-opioids>

⁵⁷⁹ Wilson, M., “Walmart to appeal dismissal of lawsuit against DOJ over opioids.” Chain Storage Age (Feb. 5, 2021). Available at <https://chainstoreage.com/walmart-appeal-dismissal-lawsuit-against-doj-over-opioids>.

- j. Pharmacy Defendant CVS failed to effectively control against diversion and undermined efforts of pharmacists to prevent diversion.
- i. CVS was the target of DEA enforcement actions that provided explicit notice of the need to investigate and resolve red flags in order to dispense controlled substances.
 - A. One of the most commonly referenced DEA enforcement decisions that appears in the Pharmacy Defendants' own documents, as part of the rules for pharmacies to follow, is the *Holiday CVS* case, discussed above.⁵⁸⁰ This case arose out of a lengthy DEA investigation and interaction between the DEA and CVS about dispensing opioids despite the red flags, in violation of the CSA. The mere fact that the case arose in Florida, rather than in Ohio or anywhere else in the country, has no bearing on CVS' responsibility to be aware of the red flags described in that case. Indeed, CVS' own Policies and Procedures say, "Employees are expected to fill and refill only legal and authorized prescriptions. They are expected to uphold this legal and moral responsibility by keeping up to date on all State and Federal changes in pharmaceutical jurisprudence."⁵⁸¹ The appearance of the *Holiday CVS* case in the NACDS summary of red flags, discussed above,⁵⁸² further confirms that all of the chain pharmacies, and especially CVS, were aware of the importance of that decision to their operations throughout the country. Because of the significance of that case, a brief review of its history is shown below.
 - B. In October 2010, Hillsborough, Florida, County Sheriff David Gee sent a letter to area CVS pharmacies, asking them "to work with law enforcement and closely scrutinize the prescriptions they receive in order to deal with the prescription drug epidemic in Florida."⁵⁸³
 - C. On December 8, 2010, the DEA hosted a meeting with representatives from CVS and the Florida Department of Health (DOH) where the DEA and DOH advised CVS that the diversion of oxycodone primarily involved fraudulent prescriptions, doctor

⁵⁸⁰ See Section §C.6.i. above.

⁵⁸¹ CVS Pharmacy Operations Manual, Policy # 000-000-000, effective date 8/98; updated 9/04/03, 12/21/04; CVS-MDLT1-000055540, at 541. It was also well-known that prescriptions were filled in Florida were diverted and transported to Ohio and other states for sale, such that CVS' violations in Florida affected those other states. See, e.g., Beall, P. "How Florida spread oxy across America." The Palm Beach Post (July 6, 2018).

<https://heroin.palmbeachpost.com/how-florida-spread-oxycodone-across-america/>

⁵⁸² See Section §C.6.i, above.

⁵⁸³ MNK-T1_0008415650 at 660.

shoppers, and unethical doctors.⁵⁸⁴ At the meeting CVS was further advised of diversion “red flags” that a pharmacy should be familiar with including “(a) many customers receiving the same combination of prescriptions (i.e., oxycodone and alprazolam); (b) many customers receiving the same strength of controlled substances (i.e., 30 milligrams of oxycodone with 15 milligrams of oxycodone and 2 milligrams of alprazolam); (c) many customers paying cash for their prescriptions; (d) many customers with the same diagnosis codes written on their prescriptions (i.e., back pain, lower lumbar, neck pain, or knee pain); and (e) individuals driving long distances to visit physicians and/or to fill prescriptions.”⁵⁸⁵ The DEA also informed CVS of a huge increase in oxycodone orders at one of its pharmacies and that in one 10 month period this pharmacy ordered 30 times more oxycodone than the typical pharmacy ordered in one year.⁵⁸⁶ Additionally, the DEA informed CVS that “verifying that the prescription was written by a physician was not the same as making an independent determination that the prescription was written for a legitimate medical purpose in the usual course of professional practice.”⁵⁸⁷

- D. On August 12, 2011, DEA hosted a second meeting with representatives from Florida CVS pharmacies.⁵⁸⁸ Once again, CVS was reminded of diversion red flags including the additional red flags of, “(f) customers coming into the pharmacy in groups, each with the same prescriptions issued by the same physician; and (g) customers with prescriptions for controlled substances written by physicians not associated with pain management (i.e., pediatricians, gynecologists, ophthalmologists, etc.)”⁵⁸⁹
- E. On October 12, 2012, DEA Administrator Michele M. Leonhart’s August 2012 Final Order revoking the DEA registrations of two Florida CVS pharmacies was published.⁵⁹⁰ The Final Order discusses several potential red flags including patients traveling long distances to the pharmacy, paying with cash, and using street names for controlled substances. The Order also discussed prescription cocktails like oxycodone and alprazolam, noting, that

⁵⁸⁴ MNK-T1_0008415650 at 658-569.

⁵⁸⁵ MNK-T1_0008415650 at 659.

⁵⁸⁶ MNK-T1_0008415650 at 660-661.

⁵⁸⁷ MNK-T1_0008415650 at 660.

⁵⁸⁸ MNK-T1_0008415650 at 661.

⁵⁸⁹ MNK-T1_0008415650 at 662.

⁵⁹⁰ Press Release, DEA, *Holiday CVS Final Order Reveals Gross Negligence By Two CVS Pharmacies In Stanford, Florida* (Oct. 15, 2012), <https://www.dea.gov/press-releases/2012/10/15/holiday-cvs-final-order-reveals-gross-negligence-two-cvs-pharmacies>

“even assuming that there are patients to whom a physician can legitimately prescribe these controlled substances simultaneously ... it is the totality of the red flags which renders them unresolvable and thus made the dispensings unlawful.”⁵⁹¹ Physician prescribing in a “factory like manner” with multiple patients being described the same drug, in the same quantities, was also discussed as a red flag.⁵⁹²

F. *Holiday CVS* was the most expansive published DEA enforcement case against CVS, but it was not the only such decision. In April 2013, CVS agreed to pay \$11 million to settle civil penalty claims for record-keeping violation under the CSA.⁵⁹³ From October 6, 2005 to October 5, 2011, CVS pharmacies in Oklahoma were alleged to have violated the CSA by “1) Creating, entering and maintaining invalid ‘dummy’ DEA registration numbers or numbers other than the valid DEA registration number of the prescribing practitioner on dispensing records, which were at times provided to state prescription drug monitoring programs; 2) Filling prescriptions for certain prescribers whose DEA registration numbers were not current or valid; and 3) Entering and maintaining CVS dispensing records, including prescription vial labels, in which the DEA registration numbers of non-prescribing practitioners were substituted for the DEA registration numbers of the prescribing practitioners.”⁵⁹⁴ More recently, in April 2019, the DEA announced that CVS had agreed to pay \$535,000 to resolve allegations that several Rhode Island pharmacies “filled thirty-nine prescriptions for Percocet, a Schedule II narcotic, that CVS pharmacists had reason to know were forged.”⁵⁹⁵

- ii. Numerous CVS Policies and Procedures, summarized below, assigned responsibility to pharmacists to exercise sound professional judgment in reviewing potential indicators of forged or altered prescriptions, and other red flags, and instructed that only legitimate prescriptions for a proper medical purpose could be filled or refilled. While these Policies and Procedures were described as “mandatory,” in fact they were not. First, some of the so called “mandatory” policies gave pharmacists a list of discretionary steps (for example pharmacists “may” consult the PDMP);

⁵⁹¹ *Holiday CVS, L.L.C., v. Holder*, Civ. No. 1:12-cv-191 (D.D.C Fed. 24, 2012).

⁵⁹² *Id.*

⁵⁹³ Press Release, Dept. of Justice, CVS To Pay \$11 Million To Settle Civil Penalty Claims Involving Violations Of Controlled Substances Act, (Apr. 3, 2013) <https://www.justice.gov/usao-wdok/pr/cvs-pay-11-million-settle-civil-penalty-claims-involving-violations-controlled>.

⁵⁹⁴ *Id.*

⁵⁹⁵ Press Release, DEA, *CVS to pay \$535,000 for filling invalid prescriptions*, (Apr. 16, 2019), <https://www.dea.gov/press-releases/2019/04/16/cvs-pay-535000-filling-invalid-prescriptions>.

and second, the reality of time pressures, and understaffing, made it impossible to follow the procedures.⁵⁹⁶

- A. An important action to detect potential illegitimate prescribing which CVS could have taken early on, but didn't, was to require pharmacists to consult the applicable State PDMP (sometimes called "PMP," or Prescription Monitoring Program) before dispensing a controlled substance, especially opioids. CVS did not *require* pharmacists to consult OARRS, nor any other State PDMP, despite the purpose of those databases to provide the type of information pharmacists would need to determine whether a red flag could be resolved, which was essential to allow a flagged prescription to be dispensed.⁵⁹⁷
- B. The State of Ohio created a PDMP in 2006, known as OARRS, and enacted regulations in 2011, to encourage greater use of OARRS by requiring a pharmacist to consult OARRS if certain "red flag"-type conditions were met.⁵⁹⁸ However, drug users could avoid detection of these conditions by shopping at multiple stores of different chains, which would prevent a prescribing pharmacist from learning whether the conditions requiring OARRS review had been met. Thus, the new and amended regulation did not address the fundamental problem that would have been solved if CVS and other chain pharmacies had made review of the PDMP/OARRS mandatory for opioids and other controlled substances.
- C. A recent review of PDMPs stated, "[M]andating that all prescribers and pharmacists enroll in PDMPs and requiring more frequent data reports would create a more unified

⁵⁹⁶ Gabler, E. "How Chaos At Chain Pharmacies Is Putting Patients at Risk." New York Times (January 31, 2020). <https://www.nytimes.com/2020/01/31/health/pharmacists-medication-errors.html>

⁵⁹⁷ See, e.g., ROPP-0059, "Suspected Forged or Altered Prescriptions", CVS-FLAG-000020192, at 20195, stating, "Compliance with this policy is mandatory," yet at 20193-94, the same ROPP lists steps which "may" be taken to investigate, including "Consulting . . . (PMP), if available."

⁵⁹⁸ Ohio Administrative Code, Rule 4729-5-20 | was amended in 2011 to make accessing OARRS mandatory only *if* the prescription/patient met any one of 5 different criteria: If a patient (1) was receiving drugs from multiple prescribers; (2) was receiving drugs for more than 12 consecutive weeks; (3) was abusing drugs (ie over utilization, early refills or appeared overly sedated or intoxicated or requested a drug using a street name, etc); (4) the prescription was issued by an unfamiliar physician or a prescriber outside the usual pharmacy geographic prescriber area; or (5) The patient resided outside the usual pharmacy geographic patient population. In November, 2015, the regulation was amended to make accessing OARRS mandatory with respect to a controlled substance, if the prescription/ patient met additional criteria: (6) if the patient adds a different or new reported drug to their therapy; or (7) An OARRS report had not been reviewed during the previous 12 months for that patient; the 2011 criteria were also still in place.

fight against drug diversion. ... Because pharmacists verify countless controlled substances every day, they can greatly affect drug diversion. Reviewing the PDMP prior to dispensing could become a part of regular workflow, regardless if a pharmacists' respected state mandates PDMP query and reporting. PDMPs may not be the sole solution to the opioid crisis or other drug diversion, but they represent progress in combatting the epidemic."⁵⁹⁹ I agree with these views. In particular, pharmacies could have, and should have, required PDMP review before dispensing prescription opioids and opioid combinations, without waiting for States to do so. At minimum, they should have analyzed their own databases to enable their pharmacists to limit diversion, by identifying prescriber-related red flags that would not have appeared in a profile of a particular patient.

- D. According to the CDC, "In 2011 and 2012 respectively, Ohio and Kentucky mandated *clinicians* to review prescription drug monitoring program (PDMP) data and implemented pain clinic regulation. In these states, MME per capita decreased in 85% and 62% of counties, respectively, from 2010 to 2015."⁶⁰⁰ It is reasonable to conclude that required PDMP review by *pharmacies* would further reduce illegitimate prescription opioid exposure.
- E. No CVS Policy or Procedure that I have reviewed makes reference to pharmacists' ability to utilize CVS' own dispensing data to assist in identifying prescriber-related red flags such as overprescribing, prescribing of higher dosages, prescribing patterns, or percentage of controlled/non controlled prescribing, I infer from the absence of such reference that CVS did not make its database available to its pharmacists for such information. Not only did CVS fail to provide such data to assist pharmacists in making red flag decisions, but instead, CVS made such decisions more difficult by imposing the following rule in the "Corresponding Responsibility" paragraph of its 2004 Policy and Procedure on Professional Practices: "*Blanket decisions based on a practitioner's prescribing habits or a customer's appearance are unprofessional and may be illegal.* Each prescription must

⁵⁹⁹ Marilyn Bulloch, The Evolution of the PDMP, Pharmacy Times (July 25, 2018), <https://www.pharmacytimes.com/view/the-evolution-of-the-pdmp>.

⁶⁰⁰ <https://www.cdc.gov/drugoverdose/policy/successes.html> (last visited July 29, 2019).

be analyzed individually to determine its merit and medical necessity.”⁶⁰¹ By requiring individualized review even in cases of pill mill-type prescribing, and by depriving pharmacists of CVS’ own data that would have identified such prescribers, CVS obstructed rather than implemented effective controls to prevent diversion.

- F. The Professional Practices policy was renamed “Professional Standards,” and updated, in February 2012, shortly after CVS’ meetings with DEA over red flag concerns; at that time, the “Corresponding Responsibility” paragraph stated that this responsibility was “especially important with regard to prescriptions for controlled drugs.”⁶⁰² This provision referred the reader to the “Protocol for Dispensing Narcotic Drugs for Pain Treatment,” for further details as to exercise of the Corresponding Responsibility of pharmacists for controlled substance dispensing.⁶⁰³
- G. CVS’ 2012 “Protocol for Dispensing Narcotic Drugs for Pain Treatment,”⁶⁰⁴ ROPP-0061, stated that pharmacists must exercise their professional judgment in deciding whether to fill a narcotic prescription, incorporating the Federal regulatory requirement that they have a “corresponding responsibility” to that of physicians to dispense medicines only for legitimate medical purposes. The ROPP provided a list of circumstances that give rise to suspicion or need for further investigation, such as practitioners who routinely prescribe the same medication in the same dosage to most or all of their patients, or who routinely prescribe the same combination of drugs for pain, “*particularly where DEA has identified that combination as potentially abused,*” (e.g. oxycodone, alprazolam, and Soma).⁶⁰⁵ However, ROPP-0061 did not require, recommend or mention the use of the PDMP or CVS’ own database to answer such questions concerning practitioners’ habits.
- H. CVS’ ROPP-0061 is cross-referenced with ROPP-0062, “Prescription Drug Monitoring Websites,” adopted April

⁶⁰¹ CVS Pharmacy Operations Manual, Policy # 000-000-000, effective date 8/98; updated 9/04/03, 12/21/04, CVS-MDLT1-000055540 at 543 (emphasis in original).

⁶⁰² CVS-MDLT1-000081508 at 512.

⁶⁰³ *Ibid.*

⁶⁰⁴ CVS-MDLT1-000081566.

⁶⁰⁵ *Id.* at 566-67 (emphasis in original).

24, 2012.⁶⁰⁶ This ROPP reiterates the “sound judgment” standard and states that a pharmacist “should” access a State’s PDMP “to augment your professional judgment when evaluating each controlled drug prescription, and should not be used as your sole determinant for filling/not filling a controlled substance.”⁶⁰⁷ Again, accessing the PDMP was not required by ROPP-0062.

- I. ROPP-0062 was updated in May 2013. The revised version informed the pharmacists that the purpose of a PDMP was to assist in preventing diversion, “strongly encouraged” pharmacists to consult the PDMP “where appropriate in making an informed decision about whether or not to fill a prescription,” and provided examples of circumstances that might lead to the decision to use the PDMP, such as the type of drug being dispensed, whether there are “red flags present,” and whether PDMP information would assist in fulfilling the pharmacist’s “corresponding responsibility.”⁶⁰⁸ Again, CVS declined to make it mandatory to consult the PDMP.
- J. ROPP-0062 was revised multiple times after 2013; consulting the PDMP was never made mandatory.⁶⁰⁹ The most recent available version of ROPP-0062 instructed pharmacists to follow state law as to when consulting the PDMP is mandatory, stating further, “In addition to following state laws, Pharmacists must also access and review PMP data whenever they identify red flags that are not able to be resolved or are reasonably certain that a person may be attempting to obtain a Schedule II-V controlled substance for a fraudulent, illegal, or a medically inappropriate purpose.”⁶¹⁰ As stated above, the PDMP itself is a primary source of information from which to identify red flags in the first place, and its value is diminished by making its use dependent on other, subjective factors that may or may not result in PDMP review by a particular pharmacist.
- K. CVS’ ROPP-0059 regarding “Suspected Forged or Altered Prescriptions,” stated that employees “must use common sense and exercise professional judgment” to decide

⁶⁰⁶ CVS-MDLT1-000081545.

⁶⁰⁷ *Id.* at 545-46.

⁶⁰⁸ CVS-MDLT1-000081477 at 477-479.

⁶⁰⁹ See, e.g., CVS-MDLT1-000081547 (July 2014); CVS-FLAG-000020985 (July 2015);

⁶¹⁰ CVS-WASHAG-00000373 at 374.

whether a prescription was legitimate, and to only fill legitimate prescriptions.⁶¹¹ Numerous factors were listed as examples of “[s]teps which *may* be used” to investigate legitimacy of a prescription, including “Consulting the state PMP, if available.” ROPP-0059 included a section entitled, “Minimizing the Likelihood of Diversion,” which provided that pharmacists “should” be familiar with diversion trends in their area and identify particular drugs and drug classes that presented higher risk of diversion, including oxycodone and hydrocodone, as well as benzodiazepines. However, while compliance with ROPP-0059 was “mandatory,” the various means of investigating red flags described in ROPP-5099 were *not* mandatory; instead, as in other CVS policies, the ROPP stated that a pharmacist “may” carry out investigations such as consulting the PDMP.⁶¹² CVS-MDLT1-000081559 at 81565(emphasis added.)

- L. The 2012 version of CVS’ ROPP-0059, (“Last review date, December 17, 2013”) also included the “Minimizing the Likelihood of Diversion” section, which again identified particular drugs and drug classes that presented higher risk of diversion, and this version specified particular benzodiazepines (alprazolam and lorazepam) as presenting higher diversion risk. However, while compliance with ROPP-0059 was “mandatory,” the various means of investigating red flags described in ROPP-5099 were *not* mandatory; instead, the ROPP stated that a pharmacist “must” use common sense, but “may” carry out investigations such as consulting the PDMP.⁶¹³ Similar distinctions between mandatory use of common sense and non-mandatory use of the PDMP were carried forward in later versions of ROPP-0059.⁶¹⁴
- M. In August 2014, CVS initiated the RxConnect Operational Prescriber Validation Policy and Procedures.⁶¹⁵ This provision outlined the system validations in place for prescriber information. Its purpose was to prevent prescriptions from being dispensed when prescriber did not have authority or had been blocked by CVS from being

⁶¹¹ CVS-MDLT1-000081559 at 560.

⁶¹² *Id.* at 561 (emphasis added).

⁶¹³ CVS-MDLT1-000081539 at 543.

⁶¹⁴ See, e.g., August 28, 2018 version, the most recent available for my review; CVS-WASHAG-00000294 at 295.

⁶¹⁵ DOC-047401; CVS-FLAG-000020264. This policy was updated without significant changes to the portion of the provision described above. E.g., CVS-FLAG-000020246 (2016); CVS-MDLT1B-000002289 (2019).

filled. The policy allowed CVS to block “prescribers who CVS, as part of corresponding responsibility, has decided not to dispense their controlled substance prescriptions.”⁶¹⁶ Contrary to the ROPP described above, effective in 2004, the 2014 policy appears to confirm that CVS had the ability to issue “blanket refusals to fill,” based on the prescriber’s behavior, regardless of patient red flags. Earlier adoption of such a policy could have blocked illegitimate opioid prescriptions from being dispensed, and also confirms that CVS’ own data enabled the company to make such determinations based on prescriber-related red flags, which could have been made accessible to pharmacists.

- N. Also in 2014, CVS adopted ROPP 047561, Federal Guidelines for Controlled Substances. The provisions included rules for intake, storage and dispensing of controlled substances, including a list of Red Flags, divided into Patient Red Flags (Distance; Cash; Suspicious Behavior; Early Fills; Doctor Shopping; Appropriateness of Therapy) and Prescriber Red Flags (Professional Practice; Cocktails; Scope of Practice; Appropriateness of Therapy). The PDMP would have been informative as to these subjects, but CVS policy did not require consulting the PDMP unless required to do so by State law. Pharmacists were “strongly encouraged,” but not required, to consult the PDMP “for new prescriptions and for prescriptions for highly diverted drugs (e.g., Hydrocodone and Oxycodone).”⁶¹⁷ Later versions required pharmacists to consult the PDMP whenever they “identify red flags that are not able to be resolved or are reasonably certain that a person may be attempting to obtain a Schedule II-V controlled substance for fraudulent, illegal or a medically inappropriate purpose,” or when required to do so by State law. Although acknowledging that such a review would provide a “more complete controlled substance use history to use their professional judgment” in deciding whether to fill the prescription or not, consulting the PDMP was not required.⁶¹⁸

⁶¹⁶ *Id.*; CVS-FLAG-000020264.

⁶¹⁷ CVS-FLAG-000020938 at 947-48.

⁶¹⁸ CVS-FLAG-000020543 at 556 (2018); CVS_WASHAG_00000390 at 403 (2019).

- O. In 2015, CVS adopted ROPP-049066: Controlled Substance Prescriber Monitoring and Review Program,⁶¹⁹ which also related to prescribers' whose behavior warranted consideration of blocking their opioid prescriptions. This program was designed to identify prescribers whose controlled substance prescriptions may be in violation of state and federal guidelines. The program aimed to further mitigate risk by resolving "red flag" prescribing trends associated with prescribers whenever possible. Elements of the program included creation of a Professional Practice team to conduct quarterly review of Tier 1 & Tier 2 Prescribers from a prescriber algorithm, as well as review and research of prescriber conduct from other sources, including state medical boards, news/media, and the DEA. Depending on the findings of the review, prescribers could be suspended from filling prescriptions at CVS stores.⁶²⁰ Such a program, including use of CVS' own data to create a prescriber algorithm, could have been implemented 15 years earlier, when the opioid epidemic was known, but less harm had been done. To the extent that the Controlled Substance Prescriber Monitoring and Review Program was successfully implemented in and after 2015, its earlier use would have prevented diversion and the risks of addiction, overdose, and mortality in prior years.
- P. In July 2018, CVS revised ROPP-0061, stating: "CVS Pharmacy pharmacists are required to document all steps taken to resolve red flags associated with controlled substance prescriptions in the patient profile. The documentation must clearly justify the determination and appropriateness of the therapy dispensed. Documentation *may* include, but it is not limited to: diagnosis, PMP check, Prescriber conversation, treatment or taper plan. Any prescriber office conversation notations must also include the person spoken to, the date and the time."⁶²¹ Consistent with past versions of the policy, and with the statement that documentation "may" include PMP check, the revised ROPP-0061 did not require checking the PDMP unless State law required it, or "when in the professional judgment

⁶¹⁹ CVS-FLAG-000020155. I have reviewed the September 2019 version, showing no significant changes. CVS-MDLT1B-000002258.

⁶²⁰ CVS-FLAG-000020155 at 155-158.

⁶²¹ CVS-WASHAG-00000359 at 361 (emphasis added).

of the Pharmacist such data would assist in making a corresponding responsibility determination.”⁶²²

- Q. The emphasis on speed and sales at the expense of patient safety was exacerbated by CVS’ incentive programs. For example, the CVS “2006 Pharmacist Incentive Plan” stated the objective, “to motivate employees to exceed top line results and maximize store profits, while maintaining high levels of customer service. . . . Incentive awards are based on actual results measured against re-established financial goals and individual performance objectives.”⁶²³ An “Incentive Opportunity” provided additional monetary compensation based on each store’s average weekly script volume, and “Rx Executables” measured the “Pharmacist’s performance against operational activities that drive pharmacy sales and store profit.”⁶²⁴ The Incentive Plan made no mention of pharmacy goals to avoid medication errors or enhance patient safety. Financial incentive plans based on profits and prescription sales inevitably conflict with the need for careful, diligent and inherently time-consuming investigation of red flags for dispensing of controlled substances, and the DEA ultimately cited such programs as contributors to the prescription opioid epidemic.⁶²⁵ I agree that these programs contributed to the epidemic and hindered, rather than helped, in the requirement of effective controls against diversion.
- R. In the absence of mandatory review of the Ohio PDMP (OARRS) and considering the typical time constraints to which pharmacists are subjected, not to mention that Ohio was experiencing an epidemic of prescription opioid misuse and mortality, it is highly likely that substantial numbers of prescriptions were misused and/or diverted and further contributed to the epidemic.
- k. Pharmacy Defendant Walgreens failed to effectively control against diversion and undermined efforts of pharmacists to prevent diversion.
- Despite policies purporting to meet requirements of a “corresponding responsibility” to assure that only legitimate prescriptions are filled, Walgreens failed to implement or enforce those policies, resulting in repeat DEA enforcement actions against Walgreens for both distribution

⁶²² *Id.* at 360.

⁶²³ CVS-MDLT1-000060949-950.

⁶²⁴ *Id.* at 951.

⁶²⁵ WAGMDL00709398.

and pharmacy violations. A brief summary of Walgreens' policies and procedures is set forth below, along with an account of the DEA enforcement actions required to address Walgreens' failure conditions that undermined the policies, including profit-based performance metrics, understaffing, and incentives for prescribing more opioids.

- ii. On August 1, 1998, Walgreens adopted a "Good Faith dispensing" policy, which stated that a pharmacist "*must* use the elements of Good Faith dispensing in conjunction with state and federal controlled substances when filling *all* prescriptions. The pharmacist must determine if a prescription for a controlled substance is dispensed for a legitimate medical purpose."⁶²⁶ The policy included a list of several "questionable circumstances," which would later be called red flags, including numbers of prescriptions from the same doctor, numbers of prescriptions sought to be filled by the same patient; unusual doses; unusual geographic distances between patient, prescriber and pharmacy; and "consistent prescr[ibing] of habit-forming drugs."⁶²⁷ A pharmacist becoming aware of one or more of such circumstances was instructed by the policy to "Not dispense the drug," and to notify the pharmacy supervisor.

- On March 24, 2003, Walgreens revised the Good Faith Practices, setting forth the same elements of Good Faith dispensing, but no longer instructing the pharmacist to "Not dispense the drug" if such circumstances were present. Instead, the revised policy instructed the pharmacist to contact the prescriber to confirm the prescription; the prescription could then be filled if the prescriber was reached and confirmed it, but was not to be dispensed if the prescriber could not be reached, or if the prescriber did not confirm the prescription.⁶²⁸ This represented a loosening of the prior policy, in that the pharmacist could dispense a controlled substance prescription confirmed by the prescriber, regardless of whether the prescriber had issued the prescription for a legitimate medical purpose. This is not simply a theoretical concern, as DEA enforcement decisions have stated that there are "circumstances in which calling the prescriber will not resolve the red flags because the red flags indicate that the prescriber is collaborating with the patient to divert drugs."⁶²⁹

- iv. Walgreens' revision dated June 18, 2004 added that a "*corresponding responsibility* rests with the pharmacist to ensure that controlled substance prescriptions are issued for a legitimate medical purpose by an individual

⁶²⁶ WAGMDL00093367 (emphasis in original).

⁶²⁷ *Id.*

⁶²⁸ WAGMDL00335012.

⁶²⁹ *Holiday CVS, L.L.C., d/b/a CVS/Pharmacy* Nos. 219 & 5195, Decision & Order, 77 Fed. Reg. 62,316, 62,318 (Oct. 12, 2012).

practitioner in the usual course of professional practice,”⁶³⁰ using the language of federal regulation Section 1306.04. Revisions in February and November 2005, and in June 2006, included similar provisions, and similarly allowed the pharmacist to dispense a controlled substance if the prescriber could be contacted and confirmed the prescription, regardless of whether the prescription was actually for a legitimate medical purpose, and to not dispense if the prescriber could not be reached or did not confirm the prescription.⁶³¹ The 2006 version changed the heading to “Good Faith Practices/Fraudulent Prescriptions,” adding instructions regarding contacting law enforcement and preservation of prescriptions upon receipt of the prescriber’s confirming that the prescription was not legitimate.⁶³²

- v. In August 2007, Walgreens adopted a policy to prevent diversion of controlled substances, directed at the risk of employees or others improperly stealing or removing drugs from the pharmacy. This provision did not alter the prior policies regarding diversion through the more common means of filling potentially illegitimate prescriptions.⁶³³
- vi. Also in 2007, Walgreens’ dispensing conduct began to attract attention from the DEA, beginning a lengthy history of CSA violations, penalties, and agreements intended to require the company to implement effective controls, and to put an end to what DEA described as “direct and significant to the epidemic of prescription drug abuse and diversion.” I agree with the DEA’s statement that Walgreens’ failures directly and significantly contributed to the opioid epidemic. Walgreens’ management entered into consent agreements with DEA regarding these violations, so there can be no doubt that corporate leadership was on notice of the absence of effective controls against diversion.
- vii. On September 30, 2009, the DEA issued an Order to Show Cause (OTSC) against a Walgreens pharmacy in San Diego, CA. The OTSC alleged that since at least January 2007 the pharmacy had been filling prescriptions from unlicensed physicians, filling prescriptions issued for other than a legitimate purpose, and otherwise dispensing controlled substances, including hydrocodone, to individuals that Walgreens knew or should have known were diverting the controlled substance.⁶³⁴
- viii. In April 2011, Walgreens entered into a three year Administrative Memorandum of Agreement with the Department of Justice and DEA,

⁶³⁰ WAGMDL00335018 (emphasis in original).

⁶³¹ WAGMDL00335018, 335024, 335010 and 19484.

⁶³² WAGFLAG00019484.

⁶³³ WAGFLDEA00000271.

⁶³⁴ WAGMDL00768976

applicable to all Walgreens pharmacies.⁶³⁵ The agreement required Walgreens to “maintain a compliance program to detect and prevent diversion of controlled substances” that would include “procedures to identify the common signs associated with the diversion of controlled substances including but not limited to, doctor-shopping and requests for early refills.”⁶³⁶ Walgreens was also required to “notify the local DEA office within two business days of a refusal to fill a prescription for controlled substances where such refusal is based on the Walgreens pharmacist's determination that the prescription was forged, altered, and/or issued for other than a legitimate medical purpose by a practitioner acting outside the usual course of professional practice.”⁶³⁷

- ix. In May 2011, shortly after Walgreens entered the April 2011 Memorandum of Agreement with the DOJ and DEA, Walgreens issued a Code of Conduct and General Training, highlighting values of “[h]onesty and integrity,” and stating a commitment to be fully compliant with federal and state laws and regulations regarding controlled substances. The Code stated, “Walgreens WILL NOT TOLERATE an illegal, unprofessional or unethical act by any team member, INCLUDING, BUT NOT LIMITED TO, THE UNAUTHORIZED SALE, POSSESSION, USE, OR DIVERSION OF CONTROLLED SUBSTANCES.”⁶³⁸ The Code informed employees that violations would be subject to discipline, including possible termination, as well as possible arrest and prosecution. In an apparent reference to the Memorandum of Agreement, the Code closed with the following: *“Affirmation: By clicking the button below, I acknowledge that as of this date, (1) I have completed one hour of General Training on the requirements imposed by Walgreens’ Corporate Integrity Agreement with HHS Office of the Inspector General and by the Walgreens Compliance Program and (2) I have received, read and understood and will abide by the Walgreens Pharmacy and Health Care Code of Conduct. I further acknowledge that I understand that my supervisor and members of the Compliance Office staff are available to answer any questions that I may have regarding the computer-based training I have received.”*⁶³⁹
- x. In October 2012, Walgreens began to develop a supplemental “Good Faith Dispensing” (GFD) policy as to a “manageable list” of “top drugs” in order to “put teeth around GFD for high risk products,” including oxycodone.⁶⁴⁰

⁶³⁵ WAGMDL00757802

⁶³⁶ WAGMDL00757802 at 803.

⁶³⁷ WAGMDL00757802 at 803.

⁶³⁸ WAGFLDEA00000127, at 127-128 (emphasis in original).

⁶³⁹ *Id.*, at 00130.

⁶⁴⁰ WAGMDL01109078

- xi. In January 2013, a Walgreens presentation stated, “In June we re-launched our Good Faith Dispensing policy. However, we have learned more about DEA's expectations around GFD and we felt the steps we were taking with GFD did not go far enough. The game has changed; we can no longer rely on the ‘I spoke to the prescriber and he said it was okay.’ This is especially true when the prescriber may be assisting the patient to inappropriately use controlled substances. We are going down a different path now and we have to make sure that we are prepared. So, we are piloting the TD GFD [Targeted Drug Good Faith Dispensing] in FL and NV.”⁶⁴¹
- xii. After pilot programs of TD GFD, including in Florida and Nevada, the TD-GFD requirement was rolled out nationwide in April 2013. As part of this roll out, Walgreens distributed a National TD GFD Policy, a Checklist, an FAQ list, set of talking points, a TD GFD powerpoint, as well as information about its National Prescriber TD-GFD efforts and a document on Clinical Pain Management.⁶⁴²
- xiii. Walgreens stated the TD GFD “policy was developed to help guide pharmacists through their corresponding responsibility in determining that the prescription was written for a legitimate medical purpose before dispensing in good faith” and was “created to assist and support pharmacists in their professional judgment to fill or refuse a target drug.”⁶⁴³ Beginning in April 2013,⁶⁴⁴ Pharmacists and Technicians were required to complete the TD-GFD checklist when dispensing prescriptions for certain “Target Drugs.”⁶⁴⁵ The “Target Drugs” were limited to single ingredient oxycodone, hydromorphone, and methadone, and the form was only to be completed for those prescriptions.⁶⁴⁶ For all “Target Drugs,” the hardcopy TD GFD checklist was required to be completed before filling the prescription. The TD GFD policy has been revised a number of times, through at least 2018.⁶⁴⁷
- xiv. In 2013, Walgreens added hydrocodone to the TD GFD checklist in limited districts but chose to wait seven years to contemplate adding it nationally.⁶⁴⁸ It was not until 2019/2020 that Walgreens internally considered adding hydrocodone as a “Target Drug” on a national scale.⁶⁴⁹

⁶⁴¹ WAGMDL00707642

⁶⁴² WAGNYAG00006361

⁶⁴³ WAGMDL01132111 at WAGMDL01132112

⁶⁴⁴ WAGMDL00316360; WAGMDL00744586

⁶⁴⁵ WAGMDL00573579

⁶⁴⁶ WAGMDL00001246; WAGMDL00001151

⁶⁴⁷ WAGMDL00005358 (attaching revised iterations)

⁶⁴⁸ WAGMDL00053720; WAGMDL00864374

⁶⁴⁹ WAGMDL00053720

At the same time Walgreens was drafting TD GFD, the DEA and FDA were in the process of finalizing the rescheduling of hydrocodone.⁶⁵⁰ Walgreens participated in a coordinated effort through the NACDS and the pharmacy community as a whole to oppose the rescheduling, citing undue burden on millions of Americans who need access to pain medications.⁶⁵¹ Walgreens omitted hydrocodone from the “Targeted Drugs”, even though it was the top ranked generic drug by retail pharmacy dollars.⁶⁵² With so many hydrocodone prescriptions and so little money per prescription due to its generic status, spending the time to properly vet each hydrocodone prescription would have impacted profitability for Walgreens and other NACDS members. Walgreens calculated that pharmacists spent approximately 5 minutes completing each checklist, equating to an average of 150 hours/store per year.⁶⁵³

- xv. Neither the 2011 MOA nor Walgreens’ new policies reduced the amount of opioids flowing out the doors. In fact, a Walgreens compliance audit found a “significant *increase* in the number of CII prescriptions we are filling,” and the company sought to “formulate a plan prior to any potential review by outside agencies.”⁶⁵⁴ On the advice of Walgreens’s CSA Compliance Officer, Dwayne Pinon, Walgreens struck two questions from the audit regarding “pain clinic patients” because as Pinon stated “If these are legitimate indicators of inappropriate prescriptions perhaps we should consider not documenting our own noncompliance.”⁶⁵⁵

Further evidence of the ineffectiveness of Walgreens GFD system was found in the massive amounts of opioids dispensed, resulting in DEA action. For example, in 2011, Florida stores were ordering so many bottles of oxy that a Walgreens CII Function Manager questioned “how they can even house this many bottle[s]”⁶⁵⁶ and discussed with the Replenishment Buyer in Pharmacy Purchasing that pharmacies were ordering an “unbelievable” amount of “1,000 bottles per week,” all of which were being dispensed.⁶⁵⁷

- xvii. Walgreens’ conduct as a distributor also resulted in DEA enforcement actions. On September 13, 2012 the DEA issued an Order to Show Cause (OTSC) and Immediate Suspension Order (ISO) to Walgreens’ Jupiter

⁶⁵⁰ CVS-MDLT1-000106705 at CVS-MDLT1-000106712, CAH_MDL2804_00011925

⁶⁵¹ JAN-MS-00837963, Rite_Aid_OMDL_0019442 , PPLP004308925

⁶⁵² CAH_FEDWV_00387846 (pg. 48)

⁶⁵³ WAGMDL00573579

⁶⁵⁴ WAGFLDEA00001890

⁶⁵⁵ WAGFLDEA00001890

⁶⁵⁶ WAGFLDEA00000852

⁶⁵⁷ WAGFLDEA00000891

Florida Distribution Center.⁶⁵⁸ The ISO stated that Walgreen's distribution center "failed to maintain effective controls against the diversion of controlled substances into other than legitimate medical, scientific, and industrial channels, in violation of 21 U.S.C. § 823(b)(1) (e)(1)."⁶⁵⁹ A DEA press release explained, "An ISO is served pursuant to Section 303 and 304 of the Controlled Substances Act, Title 21 U.S.C. § 823 and 824 when a DEA-registered business or ('registrant') constitutes an *imminent danger to the public safety and suspends a registrant's ability to handle or distribute a controlled substance such as oxycodone, hydrocodone and others pending a judicial proceeding.*"⁶⁶⁰ The DEA had previously served an Administrative Inspection (AIW) on Walgreens Jupiter and its top six retail pharmacies in Florida. "These administrative actions were to determine if these Walgreens' maintained a system in place that detects and reports suspicious orders to the DEA to prevent the diversion of control substances as governed by federal laws and the Control Substance Act relating to the proper distribution of control substances,"⁶⁶¹ and the OTSC discussed issues at the six pharmacies served by the distribution center.⁶⁶²

- xviii. The DEA's enforcement action highlighted the impropriety of Walgreens's pharmacy compensation program based on bonuses for the number of prescriptions filled, combined with efforts by Walgreens Corporate headquarters to increase oxycodone sales, which "served as an incentive for pharmacists and pharmacy technicians to ignore the 'red flags' of diversion presented by these prescriptions, many of which, in the proper exercise of the pharmacist's corresponding responsibility under 21 CFR §1306.04(a), should have resulted in a refusal to fill."⁶⁶³ The Order also described instances where Walgreens ignored ample "indications that its pharmacies were direct and significant contributors to the epidemic of prescription drug abuse and diversion" including a pharmacy continuing to dispense oxycodone to a customer who had refused to return extra units accidentally provided to him and whose girlfriend indicated was an addict who viewed the extra oxycodone as a "pot of gold," continuing to fill prescriptions for a customer who left evidence she had smoked oxycodone in the pharmacy restroom, and continuing to fill oxycodone prescriptions

⁶⁵⁸ WAGMDL00709398

⁶⁵⁹ Press Release, DEA Serves A Suspension Order On Walgreens Distribution Center In Jupiter, Florida, Drug Enforcement Administration (September 14, 2012), <https://www.dea.gov/press-releases/2012/09/14/dea-serves-suspension-order-walgreens-distribution-center-jupiter-florida>

⁶⁶⁰ *Id.*, emphasis added.

⁶⁶¹ *Id.*

⁶⁶² WAGMDL00709398

⁶⁶³ WAGMDL00709398 at 403.

for a customer who ran after learning the pharmacy had called law enforcement on the suspicion that his prescription was a forgery.⁶⁶⁴

- xix. In November 2012, the DEA served Orders to Show Cause to three Walgreens pharmacies in Florida.⁶⁶⁵ All three OTSCs reported similar circumstances of the pharmacies ignoring red flags for diversion.
- xx. On November 26, 2012, the DEA served on OTSC to a Walgreens pharmacy in Hudson, Florida, alleging that the pharmacy “ignored readily identifiable red flags that controlled substances prescribed were being diverted and dispensed controlled substances despite unresolved red flags.”⁶⁶⁶ The order noted that the pharmacy “dispensed controlled substances, primarily in suspicious cocktail combinations of oxycodone, alprazolam and carisoprodol, to patients of at least twenty (20) practitioners who were subjected to disciplinary action for dispensing illegitimate prescriptions for controlled substances. Most of these practitioners' registered locations were significant distances from [the pharmacy].” The pharmacy also filled multiple oxycodone and hydromorphone prescriptions for a customer who had previously abruptly left the pharmacy after learning the pharmacy personnel had suspected the customer of having a forged prescription.⁶⁶⁷
- xxi. On November 26, 2012, the DEA issued an OTSC to a Walgreens pharmacy in Fort Pierce, Florida.⁶⁶⁸ The DEA also alleged this pharmacy “ignored readily identifiable red flags that controlled substances prescribed were being diverted and dispensed controlled substances despite unresolved red flags.”⁶⁶⁹ The red flags ignored by the pharmacy included “multiple individuals presenting prescriptions for the same drugs in the same quantities from the same doctor; individuals with the same address presenting substantially similar prescriptions; individuals presenting prescriptions for combinations of controlled substances known to be highly abused, such as oxycodone and alprazolam; individuals presenting prescriptions for controlled substances issued by practitioners located long distances from the pharmacy; and individuals paying for prescriptions for controlled substances with cash and non-insurance discount cards.”⁶⁷⁰

⁶⁶⁴ WAGMDL00709398 at 405-406.

⁶⁶⁵ Press Release, *DEA Serves Order To Show Cause To Three Walgreens Pharmacies, Drug Enforcement Administration* (November 27, 2012), <https://www.dea.gov/press-releases/2012/11/27/dea-serves-order-show-cause-three-walgreens-pharmacies>

⁶⁶⁶ WAGMDL00387708 at 709-713.

⁶⁶⁷ WAGMDL00387708 at 709-713.

⁶⁶⁸ WAGMDL00387708 at 716-719.

⁶⁶⁹ WAGMDL00387708 at 716-719.

⁶⁷⁰ WAGMDL00387708 at 716-719.

- xxii. On November 26, 2012, the DEA issued an OTSC to a Walgreens in Oviedo, Florida, alleging that it ignored red flags of “multiple patients coming with prescriptions for the same drugs in the same quantities coming from the same doctor; patients traveling long distances to the pharmacy; patients with the same address presenting substantially similar prescriptions; and, patients presenting combinations of controlled substances known to be highly abused, such as oxycodone and alprazolam.”⁶⁷¹
- xxiii. In February 2013, the DEA served three more OTSCs on Walgreens pharmacies in Florida.⁶⁷² On February 4, 2013, the DEA issued an OTSC to a Walgreens in Oviedo, Florida, alleging that it ignored red flags of “multiple individuals presenting prescriptions for the same drugs in the same quantities from the same doctor; individuals with the same address presenting substantially similar prescriptions; individuals presenting prescriptions for combinations of controlled substances known to be highly abused, such as oxycodone and alprazolam; individuals presenting prescriptions for controlled substances issued by practitioners located long distances from the pharmacy; individuals paying for prescriptions for controlled substances with cash and non-insurance discount cards; individuals residing long distances from the pharmacy; and individuals residing long distances from the practitioners from whom the prescriptions were obtained.”⁶⁷³
- xxiv. On February 11, 2013, served an OTSC to a Walgreens pharmacy in Fort Pierce, Florida, alleging it dispensed controlled substances despite red flags of “multiple individuals presenting prescriptions for the same drugs in the same quantities from the same practitioner; individuals presenting prescriptions for combinations of controlled substances known to be highly abused, such as oxycodone and benzodiazepines; individuals presenting prescriptions for controlled substances issued by practitioners located long distances from the pharmacy; individuals presenting prescriptions for controlled substances issued by multiple practitioners, or

⁶⁷¹ WAGMDL00387708 at 722-726.

⁶⁷² Press Release, DEA Serves Another Walgreens Pharmacy An Order To Show Cause, Drug Enforcement Administration (February 6, 2013), <https://www.dea.gov/press-releases/2013/02/06/dea-serves-another-walgreens-pharmacy-order-show-cause>;
 Press Release, DEA Serves An Order To Show Cause On Walgreen’s Pharmacy In Fort Pierce, Drug Enforcement Administration (February 12, 2013), <https://www.dea.gov/press-releases/2013/02/12/dea-serves-order-show-cause-walgreens-pharmacy-fort-pierce>;
 Press Release, *DEA Serves An Order To Show Cause On Walgreen’s Pharmacy In Fort Myers*, Drug Enforcement Administration (February 22, 2013), <https://www.dea.gov/press-releases/2013/02/22/dea-serves-order-show-cause-walgreens-pharmacy-fort-myers>

⁶⁷³ WAGMDL00387708 at 729-738

‘doctor shoppers’; and warnings documented by pharmacy employees regarding physicians prescribing illegitimately.”⁶⁷⁴

- xxv. On February 19, 2013, DEA served an OTSC to a Walgreens pharmacy in Fort Meyers, Florida, alleging the pharmacy filled numerous controlled substance prescriptions despite customers exhibiting red flags including “multiple individuals presenting prescriptions for the same drugs in the same quantities from the same doctor; individuals with the same address presenting substantially similar prescriptions; individuals presenting prescriptions for combinations of controlled substances known to be highly abused, such as oxycodone, alprazolam and carisoprodol; individuals from out-of-state or who had travelled significant distances within state to fill prescriptions at [the pharmacy]; and filling new oxycodone prescriptions for customers when fewer than 30 days had elapsed since the customer had filled their previous prescription for a 30-day supply of oxycodone.”⁶⁷⁵
- xxvi. In June 2013, Walgreens entered into a three year Memorandum of Agreement with the Department of Justice and DEA that included \$80 million in civil penalties (the largest in DEA history at the time) to resolve the DEA’s administrative actions and investigation regarding the Florida distribution center and pharmacies.⁶⁷⁶ The “Covered Conduct” encompassed by the Agreement included the failures to establish effective controls against diversion or report suspicious orders at the Distribution Center, as well as the pharmacies’ failure to exercise their “corresponding responsibility to ensure that controlled substances were dispensed pursuant to prescriptions issued for legitimate medical purposes by practitioners acting in the usual course of their professional practice, as required by 21 C.F.R §1306.04(a).”⁶⁷⁷ The June 2013 agreement superseded the obligations of the 2011 Memorandum of Agreement,⁶⁷⁸ and required Walgreens to “maintain a compliance program in an effort to detect and prevent diversion of controlled substances.”⁶⁷⁹ Walgreens also committed to “continue to enhance its Good Faith Dispensing Policy and training materials to identify “red flags” of potential diversion for pharmacists to consider in making professional judgments regarding dispensing of controlled substances” and “train its pharmacy personnel at least annually on Good Faith Dispensing and will update the Good Faith Dispensing

⁶⁷⁴ *Id.* at 740-743.

⁶⁷⁵ *Id.* at 746-751.

⁶⁷⁶ WAGMDL00490963; Press Release, U.S. Attorney’s Office S. Dist. of Fla., *Walgreens Agrees To Pay A Record Settlement Of \$80 Million For Civil Penalties Under The Controlled Substances Act* (June 11, 2013), <https://www.justice.gov/usao-sdfl/pr/walgreens-agrees-pay-record-settlement-80-million-civil-penalties-under-controlled>.

⁶⁷⁷ WAGMDL00490963 at 966.

⁶⁷⁸ *Id.* at 967, paragraph 3.

⁶⁷⁹ *Id.* at 968.

Policy and training materials to respond to changing diversion threats of which Walgreens is aware.”⁶⁸⁰

- xxvii. Despite removing controlled substances from the bonus calculations in 2014, Walgreens continued to incentivize speed in filling prescriptions and diminishing the time available to detect and resolve red flags, by using a metric of “Rx/day” to calculate bonuses.⁶⁸¹, which inherently prioritized speed in filling prescriptions and reduced the time available to detect and resolve red flags.
- xxviii. A December 2014 audit performed after the 2013 DEA settlement found continuing supervision and compliance failures. The audit team found no formal monitoring program existed to confirm that pharmacies across the chain were complying with controlled substance documentation and retention requirements; no monitoring outside of the inadequate “store walk program” existed to monitor TD GFD requirements; and employees were failing to timely complete Good Faith Dispensing training, such that, at the time of the audit, over 35,000 employees had not completed their required training for that year.⁶⁸²
- xxix. In June and July 2015, Walgreens performed an audit of a random sample of approximately 2,400 pharmacies to determine whether Walgreens was “compliant with the policies/procedures put in place” regarding dispensing pursuant to Walgreens’s agreement with the DEA.⁶⁸³ As the audit progressed, Walgreens documents state that the audits were “not going great,” and that they would need to implement a “mitigation plan... to satisfy the MOA [Memorandum of Agreement]” for the non-compliance revealed by the audit.⁶⁸⁴ Walgreens concluded that the audit “Results were unfavorable.”⁶⁸⁵ Fewer than 60% of stores were in compliance with TD GFD for filled prescriptions; 1,160 stores did not have a single refused prescription in a nine month period,⁶⁸⁶ an indicator that prescriptions were undoubtedly dispensed despite unresolved red flags.
- xxx. Failure to prevent inappropriate dispensing likely occurred, in part, due to Walgreens’ imposition of “performance metrics,” as discussed below. In short, performance metrics assess whether pharmacists are meeting goals that are largely driven by profits and numbers of prescriptions filled. For example, in February 2012, Richard Ashworth, then the Vice President of

⁶⁸⁰ WAGMDL00490963 at 977.

⁶⁸¹ FY19 Business Planning – Pharmacy & Retail Operations; WAGMDL00706531.

⁶⁸² WAGMDL00674321

⁶⁸³ WAGMDL00037616 at slide 3; WAGFLAG00092402 (RXI June BCI questions with sources)

⁶⁸⁴ WAGMDL00045962

⁶⁸⁵ WAGMDL00037616 at 37618; *See also* WAGMDL00487576

⁶⁸⁶ WAGMDL00037616

Walgreens' Western Division, supervising over 2,000 Walgreens stores, encouraged stores "to drive for the activities that drive incremental scripts. There are metrics we can improve, today, that we will demonstrate the 'doing whatever it takes' to achieve 100% of FY2011 Script volume," noting "we are not doing whatever it takes," and particularly that in the "Top 2 complaints" was "Pharmacy Fill was denied."⁶⁸⁷

- xxxi. Walgreens' internal documents show the stress and strain reported by employees due to the imposition of such metrics. A March 2013 document outlining Pharmacy Managers' feedback on current challenges stated that pharmacists did not have enough time to do the multiple tasks assigned to them, and that a lack of resources kept them from being effective and consistent.⁶⁸⁸ Pharmacy managers also stated that they were "[s]truggling to keep our heads above water let alone manage."⁶⁸⁹
- xxxii. Rx Supervisor Workload Feedback notes dated May 24, 2013, stated that Pharmacy Supervisors spend as much as 3-4 hours/week answering complaints related to Good Faith Dispensing, which impacted time spent performing any other responsibilities.⁶⁹⁰ The notes also stated that some stores were responsible for making an unrealistic amount of patient calls, sometimes over 100 phone calls per day.⁶⁹¹ Those notes went on to point out that pharmacy supervisors had been asked to visit hospitals to suggest Bedside Delivery and that "[a]ll RXS on the call felt that tasks are continually being added to their plate and no activities are being taken away. It makes it extremely tough to manage these new tasks in addition to store walks and other daily responsibilities."⁶⁹²
- xxxiii. In December 2016, the Chicago Tribune reported that Walgreens pharmacists, when filling prescriptions, missed 1 in 3 - 30% - of drug interactions, dispensing medication without warning patients of the risk of potentially dangerous or even fatal side effects of the co-prescribed drugs.⁶⁹³ The investigation found that "pharmacists frequently race through legally required drug safety checks, including whether the dose is reasonable and whether the medication might interact with other drugs the patient is taking." In response to the article, Walgreens admitted it collects business metrics to monitor staffing levels and service, but denied

⁶⁸⁷ WAGMDL00974032

⁶⁸⁸ WAGMDL01166994

⁶⁸⁹ WAGMDL01166994

⁶⁹⁰ WAGMDL01166882

⁶⁹¹ WAGMDL01166882

⁶⁹² WAGMDL01166882

⁶⁹³ WAGNMAG00009844 at WAGNMAG00009850; Sam Roe et al., Pharmacies Miss Half of Dangerous Drug Combinations, Chi. Tribune (Dec. 15, 2016), <https://www.chicagotribune.com/investigations/ct-drug-interactions-pharmacy-met-20161214-story.html>

using them “in a manner that emphasizes productivity over patient safety.” Walgreens “said it would provide additional training on drug interactions” for its pharmacists and would work to move “administrative tasks out of stores and to a centralized office” to “give pharmacists more time to help patients.”⁶⁹⁴

- xxxiv. Walgreens internally discussed the testing used by the investigation and the report.⁶⁹⁵ In each instance, the drug interaction should have triggered a “Major DUR.” While none of the tests were for a “cocktail drug” combination (i.e. opioids plus another problematic controlled substance), the Major DUR was the same internal red flag mechanism used by Walgreens for flagging cocktail drugs. For the Tribune investigation, a pharmacy “passed” the test if the pharmacist *either* called the doctor *or* counseled the patient when presented with the drug combination.⁶⁹⁶ Walgreens “passed” 19 out of 30 tests.
- xxxv. Walgreens also internally discussed that, in response to the report, Carmen Catizone, executive director of the National Association of Boards of Pharmacy, previously told the Tribune he would like to see all states require pharmacists to provide counseling about first-time medications and changes of doses. Catizone also said authorities should examine whether to set minimum staffing levels for pharmacies to address workload issues. Pharmacies sometimes have to fill hundreds of prescriptions a day. He said he wants states to publicly disclose pharmacy medication errors. In addition, he said, authorities should examine whether to set minimum staffing levels for pharmacies to address workload issues.⁶⁹⁷
- xxxvi. On February 16, 2018, Walgreens pharmacist Robert Jaeger wrote an email to inform Walgreens that store managers had challenged and attempted to override his “refusal to fill a prescription for a C2 medication,” and that such conduct was part of a larger problem.⁶⁹⁸ In my opinion, Mr. Jaeger’s account calls into serious question the “Good Faith” in Walgreens’ “Good Faith Dispensing,” and highlights, instead, the inherent conflict between profit and pleasing customers, on the one hand, and the “corresponding responsibility” to fill only prescriptions for a legitimate medical purpose, on the other. I agree with Mr. Jaeger’s conclusion that this conflict results in filling of illegitimate prescriptions that have contributed to the opioid epidemic. Salient portions of Mr. Jaeger’s detailed account are excerpted below:

⁶⁹⁴ *Id.*

⁶⁹⁵ WAGMDL00250895

⁶⁹⁶ WAGMDL00250895 at slide 3

⁶⁹⁷ WAGMDL00250895 at slide 4, presenters notes

⁶⁹⁸ WAGCASF00046096 (emphasis in original)

- A. On January 15, 2018, Mr. Yaeger refused to fill a prescription for a C-II medication, following the Walgreens policy regarding “good faith dispensing.” One of the red flags Mr. Yaeger identified was that “the patient threatened me.” The customer was upset and “made numerous complaints to the company.” A number of store managers were at Mr. Yaeger’s store for a meeting that day. Two of the managers from other stores challenged Mr. Jaeger’s decision, stating, “if the prescription is not being filled early and the dose is within safe limits, you cannot not refuse to fill the prescription,” and denying that the customer’s behavior could be a cause not to dispense. According to Mr. Jaeger’s complaint, he was told that “a store manager representing the Walgreens Company and my superior, is the authority in cases of determining when to fill prescriptions for controlled substances including opiates.” He described the managers’ behavior as “extremely intimidating and persuasive.” Mr. Jaeger informed the managers that the customer had threatened to call his supervisor, and that DEA guidance included assertive and abusive behavior as a red flag. The managers disagreed and stated that customer behavior was not considered in the GFD policy.
- B. Mr. Jaeger’s email noted the conflict between managers wanting to avoid complaints that affect their bonuses, and the need to follow the law, stating, *“As long as Walgreens allows their pharmacists to be evaluated by store managers (who are trained by the Company to be concerned with profit, customer service, and resolving customer complaints), store managers will assert their authority over the pharmacists and will naturally confuse good faith dispensing issues with customer service issues. This is a clear conflict of interest.”*
- C. Mr. Jaeger continued, “please do not mistake this as an isolated event and treat it as such. I have now recently had 3 store managers, a district manager, and a pharmacy supervisor lay down resistance when I refused to fill a prescription. I was even threatened with being insubordinate when I resisted. I also know many other pharmacists, both currently working for the Company and others who have since left, who have felt the same pressure, either by being directly told or to have resistance placed on them, to fill prescriptions that went against their own professional judgment. All pharmacists were also given training at the district office to offer guidance on good faith dispensing. Some who led the discussion were not even pharmacists, but rather were people in a position of authority who also perceive personal gain and profit for the Company if the pharmacists continue to fill controlled substances without questioning their legitimacy. The take home message of the meeting was to lean more toward

dispensing and not refusing to fill prescriptions for controlled substances. Let me point out that during the meeting there were several scenarios that were given in which a prescription for a controlled substance was brought into the pharmacy. Some scenarios had "red flags." In all but one scenario it was concluded by the people conducting the meeting that we should just go ahead and fill the prescription."

- D. Mr. Jaeger documented other troubling incidents of a similar nature: "The other day I refused to fill a controlled prescription for a patient for obvious multiple red flags. I made documentation and I flagged the patient's profile so as to prevent other Walgreens pharmacies from filling it. I even told the patient his prescription would not be welcomed by any Walgreens. It got filled anyway at a Walgreens pharmacy, against company policy."
- E. Mr. Jaeger's email concluded, "This was not handled correctly the first time I brought it to the attention of the Company. Although I received an apology, the reality is that nothing has changed and the problem inherent in the system was not corrected. It was treated as an isolated incident. *It is my expectation that Walgreens Boots Alliance, Inc. upholds its own policies and adheres to its Code of Conduct and Business Ethics and does the right thing by correcting this conflict of interest because it directly contributes to the diversion of controlled substances and to the deaths of tens of thousands of Americans from drug overdose abusing dangerous prescription drugs. How many of these deaths can be accounted for by controlled substances furnished at a Walgreens Pharmacy?"*

xxxvii. In approximately December 2019, Walgreens retained Tata Consulting Services (TCS), to look into a number of Walgreens' issues, including stress levels among pharmacists. In or around December 2019, Tata Consulting Services (TCS) performed an analysis of certain issues related to Walgreens's pharmacies, including stress levels among pharmacists.. As reported by the New York Times in February 2020:⁶⁹⁹ "Pharmacy employees at Walgreens told consultants late last year that high levels of stress and 'unreasonable' expectations had led them to make mistakes while filling prescriptions and to ignore some safety procedures. But when the consultants presented their findings at Walgreens's corporate offices this month, there was no reference to the errors and little mention of other concerns the employees had raised. That's because senior leaders at Walgreens had directed the consultants to remove some damaging findings after seeing a draft of their presentation, a review of internal

⁶⁹⁹ Gabler, E. "How Chaos At Chain Pharmacies Is Putting Patients at Risk." New York Times (January 31, 2020). <https://www.nytimes.com/2020/01/31/health/pharmacists-medication-errors.html>

emails, chat logs and two versions of the report shows. In one instance, Amy Bixler, the director of pharmacy and retail operations at Walgreens, told them to delete a bullet point last month that mentioned how employees ‘sometimes skirted or completely ignored’ proper procedures to meet corporate metrics, according to the chat logs and the draft report. A slide detailing ‘errors resulting from stress’ was also removed. The consultants, a group from Tata Consultancy Services that was examining the company’s computer system for filling prescriptions, had included the slide among their ‘high level findings.’ ... The pharmacy chains have pushed back on the complaints, saying staffing was sufficient and errors were rare. Walgreens told The Times that its pharmacists knew ‘they should never work beyond what they believe is advisable.’ But the consultants heard similar complaints in interviews with workers at eight Walgreens pharmacies last year. Both versions of the consultants’ report noted ‘a widespread perception that there is not enough time to respond to all pharmacy tasks.’ In the deleted slide on stress-related errors, the consultants wrote, ‘We were told that pill bottles had been found to contain more than one medication.’ They said they ‘heard multiple reports of improper behavior that was ‘largely attributed to the desire’ to meet a corporate metric known as ‘promise time,’ which ensures that patients get prescriptions filled within a set amount of time. The Times reported last month that such metrics often factor into employee bonuses and performance reviews. The final presentation was delivered about two weeks ago at the drugstore chain’s corporate campus in Deerfield, Ill. The consultants had been seeking approval of the research report from various departments at Walgreens. They have since moved to the next step in the project — improving the pharmacy’s computer system.

xxxviii. Early drafts of the Tata presentations include slides with troublesome findings, some of which were included in later drafts, but some of which were deleted or significantly softened at Walgreens’s request.⁷⁰⁰ Tata employees noted that some of the requests to remove information from slides conflicted with their business ethics.⁷⁰¹ Below are some of the more significant slides from version 3 of the report:⁷⁰²

⁷⁰⁰ WAGMDL01109276

⁷⁰¹ WAGMDL01109276

⁷⁰² See TCS00000196 (Version 3) as compared to TCS00000396 (Version Six)

HIGH VARIATION IN PERCEPTION OF PHARMACY EFFICIENCY**Significant gaps in trust**

- There was widespread mistrust of inventory numbers both when reported by the system and other staff members
- A majority of Pharmacists we spoke with thought they understood laws and regulations better than the system
 - The Pharmacy Managers suggested that such confidence was misplaced and that it is easy for misunderstandings to spread and persist in individual pharmacies
- It was reported that improper overrides for coupons occurred because users did not trust the system to properly process coupons and trusted their understanding of the coupons system more
- Users reported that they felt their coworkers were less capable or knowledgeable than them, with the exception of new hires
 - This was true markedly true between more senior Technicians and Pharmacists, with Technicians suggesting that they are more important to keeping the pharmacies running and Pharmacists suggesting that they have to cover for Technician errors

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TCS0000022

HIGH STRESS**Errors resulting from stress**

- We heard multiple reports of improper behavior which was largely attributed to the desire to keep below promise time
 - We were told that pill bottles had been found to contain more than one medication
 - We also heard that prescriptions returned to the shelf were sometimes poured back into the stock bottles, including one instance of this occurring with a liquid medication
- All participants expressed a high level of stress in trying to meet promise time and the belief that, given current levels of staffing, promise time was unreasonable while following proper procedure
 - Two participants claimed that they don't believe that the corporate teams care for them and are too focused on promise time
 - One said that they are concerned about taking their lunch break as they feel they are judged for not making promise time following the lunch break and cut their break short

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USER PERCEPTIONS**Users are typically responsive instead of proactive**

- There is a widespread perception that there is not enough time to respond to all pharmacy tasks
 - Proper procedures are sometimes skirted or completely ignored due to worries of meeting promise time
 - These can be as serious as returning medication to stock bottle instead of properly restocking
- Users prioritize task comfort due to the perception that engaging in new or unfamiliar tasks will drag down pharmacy performance
 - In the long term this reduces user skill and significantly impacts pharmacy efficiency
- Unusual task load or unexpected changes in the pharmacy environment are very disruptive to less efficient pharmacies
 - Not enough buffer time to accommodate such changes

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TCS00000253

USER PERCEPTIONS**Users believe that corporate doesn't understand their needs**

- When there is not a strong leadership voice users think that corporate expectations are impossible to achieve
 - Promise time is thought to be unreasonable given necessary tasks
 - Training is seen as insufficient prior to working in the pharmacy
 - Users expect that turnover is unsustainable given then learning curve of new Technicians
- Users feel that the issues with IC Plus and Core Workflow should be obvious and easy to solve
 - Hard separation of information across windows, tabs, and Store Net is seen as arbitrary and unnecessary
- Many tasks, such as responding to patient calls, are seen as a waste of time that should be handled in other ways

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TCS00000254

Age Group	U.S. should take action	U.S. should take strong action
18-29	95%	90%
30-49	95%	90%
50-69	95%	90%
70+	95%	90%

-151-

Lembke Report

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Lembke Report

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[REDACTED]

[REDACTED]

738

[REDACTED]

735 [REDACTED]
736 [REDACTED]
737 [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[illegible][illegible]

[REDACTED]

- [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]

- i. Giant Eagle is a grocery store chain with approximately 125 locations in Ohio, Western Pennsylvania, Maryland, Indiana, and West Virginia.⁷⁴³ The chain began adding “store-within-a-store” pharmacies in the 1980s.⁷⁴⁴
- ii. Giant Eagle’s history of controlled substance policies and procedures is minimal by comparison to those of the other Pharmacy Defendants discussed previously. For example, Giant Eagle did not adopt a Controlled Substance Dispensing Guideline until July 22, 2013, long after the prescription opioid epidemic had been in existence.⁷⁴⁵
- Giant Eagle’s 2013 Dispensing Guideline described red flags for combination prescribing as follows: “(1) prescriptions written together for: oxycodone/hydrocodone (opiate) + alprazolam (benzodiazepine) + carisoprodol (muscle relaxant as a potentiator)” and (2) “multiple prescriptions for the strongest formulations of hydrocodone and alprazolam.”⁷⁴⁶ This Guideline was seriously erroneous, since any combination of an opioid and a benzodiazepine should have been a red flag for many years prior to 2013, based on the medical literature and DEA enforcement decisions described previously.⁷⁴⁷ The red flag should not have required the presence of a muscle relaxant, nor should it have limited the opioid component to “multiple prescriptions for the strongest formulations of hydrocodone,” nor should it have limited the benzodiazepine component to alprazolam (Xanax) or the “strongest formulations” of Xanax. To the extent that Giant Eagle’s pharmacists paid attention to the 2013 policy, it is highly likely that high risk cocktails of opioids plus benzodiazepines would have been improperly dispensed without a red flag or investigation. Of course, prior to the adoption of the Guideline in 2013, such cocktails would have been improperly dispensed without question, unless the individual pharmacist chose to interpose a red flag in the absence of any Guideline instructing that to be done.
- iv. Far from making consultation of a PDMP mandatory, Giant Eagle’s Controlled Substance Dispensing Guideline instead interposed an obstacle to such access, by instructing that “the Pharmacist *must have cause* before accessing the PDMP” and “when accessing a PDMP note the date and reason for accessing the database.”⁷⁴⁸ In my opinion, whether or not to dispense a prescription opioid is the only “cause” that a pharmacist should have needed to consult a PDMP such as OARRS, which was designed specifically to provide doctors and pharmacists with information needed to prevent diversion and save lives.

⁷⁴³ Giant Eagle. (2021, March 12). In *Wikipedia*. https://en.wikipedia.org/wiki/Giant_Eagle#Giant_Eagle_Pharmacy

⁷⁴⁴ *Id.*

⁷⁴⁵ HBC_MDL00191292

⁷⁴⁶ Giant Eagle, Pharmacy Controlled Substance Dispensing Guideline, HBC_MDL00191292

⁷⁴⁷ See Section §C.6.g.

⁷⁴⁸ HBC_MDL00191292, at 1293.

- v. According to internal documents from 2012 and 2014, Giant Eagle's Bonus Plan was based primarily on Prescription Unit Volume and Profitability, with a smaller component based on "Customer Satisfaction" ratings. A larger bonus applied to larger numbers of units prescribed by the pharmacist. The Plan did not distinguish between scheduled and non-scheduled drugs, thereby incentivizing Giant Eagle's pharmacists to increase earnings by maximizing exposure to addictive and dangerous opioids. From 2015 on, the Bonus Plan was entirely based on prescription volume and profitability, with no customer service component.⁷⁴⁹
- vi. In December 2011, Giant Eagle entered into a Settlement Agreement with the Ohio Board of Pharmacy related to its failure to deter and detect the theft and diversion of controlled substances at its Chardon, Ohio pharmacy. From May 1, 2009 through January 21, 2011, a pharmacy technician diverted controlled substances including hydrocodone, to "her addicted husband and also sold to another individual."⁷⁵⁰
- n. In summary, the Pharmacy Defendants were far more than unwitting pill dispensers. Instead, they actively participated in efforts to increase the opioid supply while ignoring the many warning signs of a growing opioid problem, and as such were central drivers of the opioid epidemic. As the "last line of defense" against opioid misuse and diversion, these Defendants failed miserably.

7. No reliable scientific evidence shows that long-term opioid therapy is effective for chronic non-cancer pain.

- a. Through the aforementioned methods, and by relying on flawed and industry-backed studies, the Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including overstatement of benefits of long-term use for chronic pain. In fact, there is not, and has never been, reliable evidence that long-term opioid use improves pain or function to any clinically meaningful degree.
- b. The best evidence available suggests that there is little or no improvement in pain or function for most patients on long-term opioid therapy. The Industry further claimed that the failure to prescribe opioids led to the "undertreatment of pain." Whether or not pain was undertreated does not change the fact that prescription opioids are an inappropriate method to address that concern, due to the absence of evidence of long-term benefit, and the strong evidence of unacceptable risk.⁷⁵¹

⁷⁴⁹ HBC_MDL00191120, HBC_MDL00191122, HBC_MDL00191127, HBC_MDL00191129, HBC_MDL00191162, HBC_MDL00191178, HBC_MDL00191181.

⁷⁵⁰ BOP_Internal_000000130

⁷⁵¹ As stated in the NASEM 2017 Report, "The very real problems of underdiagnosis and undertreatment of pain are valid concerns, but *it would be a mistake to infer that greater utilization of opioids would ameliorate these problems,*" due to the lack of evidence that opioids provide long-term benefits for chronic pain. NASEM Report (2017), fn. 51, above, at p. 51. (emphasis added).

Patients often endorse ongoing subjective benefit from the opioid, not because it is treating underlying pain, but because it is relieving the pain of opioid withdrawal from the previous dose. Studies show that pain improves when patients on chronic high dose opioid therapy reduce their dose or come off opioids. Limiting opioid prescribing is good medicine, because it decreases exposure to a dangerous and potentially lethal drug, without compromising pain treatment.

Study	YEAR	TYPE OF PAIN	LACK OF EVIDENCE
Chou R , et al.,. Clinical Guidelines for the use of chronic opioid therapy in chronic noncancer pain. <i>Journal of Pain</i> . 2009;10(2):113-130 at p. 130.e5.	2009	Chronic non-cancer pain	"insufficient to assess effects on health outcomes"
Noble M ., et al. Long-term opioid management for chronic noncancer pain. <i>Cochrane Database Syst Rev</i> . 2010;(1):CD006605. doi:10.1002/14651858.CD006605.pub2, p. 2.	2010	Chronic non-cancer pain	"weak" evidence "Whether quality of life or functioning improves is inconclusive."
Chaparro LE , et al. Opioids compared to placebo or other treatments for chronic low-back pain. <i>Cochrane Database Syst Rev</i> . 2013. doi:10.1002/14651858.CD004959.pub4	2013	Chronic low-back pain	"does not support that opioids are more effective than other groups of analgesics"
da Costa BR , et al. Oral or transdermal opioids for osteoarthritis of the knee or hip <i>Cochrane Database Syst Rev</i> . 2014	2014	Osteoarthritis pain (knee or hip)	"may have deleterious effects and do not seem to improve pain relief"
Chou R ., et al. The Effectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop. <i>Ann Intern Med</i> . 2015;162(4). doi:10.7326/M14-2559, at p. 276	2015	Chronic pain	"Evidence is insufficient to determine the effectiveness of long-term opioid therapy for improving chronic pain and function."
Krebs EE ., et al. Effect of opioid vs non-opioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain the SPACE randomized clinical trial. <i>JAMA - J Am Med Assoc</i> . 2018. doi:10.1001/jama.2018.0899	2018	Chronic back pain; Osteoarthritis pain (knee or hip)	"no benefit of opioids over non-opioid medication"
Welsch P , et al. Opioids in chronic noncancer pain-are opioids superior to nonopioid analgesics? : A systematic review and meta-analysis. <i>Schmerz</i> . 2015. doi:10.1007/s00482-014-1436-0, at p. 3.	2015	Chronic low-back pain	"weak evidence"
Rosenberg JM , et al. Opioid Therapy for Chronic Pain: overview of the 2017 US Department of Veterans Affairs and US Department of Defense clinical practice guidelines. <i>Pain Medicine</i> . 2018;19:928-941, at p. 930	2018	Chronic pain	"little evidence of benefit for long-term opioid use"
Bonnie R . et al. Pain Management and the Opioid Epidemic Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use. <i>NASEM</i> . 2017. Washington, DC: The National Academies Press. doi: https://doi.org/10.17226/24781	2017	Long-term pain	"lack of evidence that the drugs are effective for long-term pain management"
Busse JW , et al. Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. <i>JAMA</i> . 2018;320(23):2448-2460. doi:10.1001/jama.2018.18472	2018	Chronic pain	Failure to meet test of Minimally Important Difference in pain relief compared to placebo; no difference between opioids and non-opioids for pain relief.

- c. As summarized in the table above, scientific evidence of prescription opioids' benefit for chronic pain has been repeatedly described as "weak," or "inconclusive." Randomized, placebo-controlled clinical trials, generally 12 weeks or less, were too brief to support claims of long-term benefit, and non-randomized trials do not provide reliable evidence of efficacy. Such evidence was inadequate to support the widespread use of the drugs and the risks they imposed. Even the 2009 Guidelines promulgated by advocacy groups funded by the Pharmaceutical Opioid Industry admitted that evidence regarding chronic opioid therapy was "insufficient to assess effects on health outcomes."⁷⁵² Twelve-week studies of opioids are insufficient to assess their risks and benefits, for the following reasons:
- i. Prescription opioids differ from other pain medications in important ways. In addition to providing acute pain relief, opioids also have unintended psychotropic effects (improved mood, increased energy, decreased anxiety), which make them more likely to be reinforcing and to lead to addiction. Patients with chronic pain can find opioids reinforcing, independent of whether they provide pain relief.⁷⁵³ Although addiction to opioid painkillers can occur quickly in some individuals, for others, addiction may take weeks, months, or years to manifest, and duration of exposure is the most significant risk factor for addiction (*see* discussion of Edlund study, above). Hence, a true assessment of the risks of highly addictive drugs like opioid pain relievers (the molecular equivalent of heroin) requires a longer period of study than 12 weeks.
 - ii. According to a study of combat injury victims among military personnel, 6.8% developed an opioid addiction after a short-term prescription of opioids (within a 7-day discharge window). The median time to diagnosis of the opioid use disorder was 3 years.⁷⁵⁴ The authors state that this was "the first study to show that persistent opioid use after trauma is associated with the development of clinically recognized opioid abuse years after the initial injury."⁷⁵⁵ The long median time to diagnosis of opioid addiction reinforces the conclusion that industry-sponsored studies claiming a low risk of addiction are far too brief to provide reliable, real-world estimates of risk.⁷⁵⁶

⁷⁵² Chou R. Clinical Guidelines for the use of chronic opioid therapy in chronic noncancer pain. *Journal of Pain*. 2009;10(2):113-130 at p. 130.e5.

⁷⁵³ Matthias M, Donaldson MT, Jensen AC, Krebs EE. "I was a little surprised": Qualitative Insights from Patients Enrolled in a 12-Month Trial Comparing Opioids to Non-Opioid Medications for Chronic Musculoskeletal Pain. *J Pain*. 2018: 1-9, at p. 1.

⁷⁵⁴ Beyer CA, Poltavskiy E, Walker LE *et. al.*, Persistent Opioid Use After Combat Injury and Subsequent Long-term Risk of Abuse: a retrospective cohort study. *Annals of Surgery*, 2019; 1-9, at p. 1.

⁷⁵⁵ *Id.* at p. 3.

⁷⁵⁶ See discussion of industry-sponsored studies of addiction risk at Section §C.8, below.

- Naliboff *et al.*, in their two-arm, randomized, pragmatic clinical trial comparing stable dose to escalating dose of opioid medications among 135 patients at a VA clinic in Los Angeles, “carefully selected” as appropriate candidates for chronic opioid therapy, nevertheless discharged 27% of patients over the course of the study due to opioid misuse/noncompliance.⁷⁵⁷ Urine toxicology screens were included in the protocol.⁷⁵⁸ The authors concluded, “Overall, this study confirms that even in carefully selected tertiary-care patients, substance misuse is a significant problem. Importantly, *40% of these misuse problems did not become apparent within the first 6 months, pointing out the need for studies of longer duration.*”⁷⁵⁹ (emphasis added). These data also support the need for ongoing monitoring for misuse and addiction in patients prescribed opioids long-term.
- iv. There are serious and certain risks associated with long-term opioid therapy, including but not limited to tolerance, dependence, withdrawal, opioid induced hyperalgesia (increased pain caused by opioids), immunosuppression, serious constipation, depression, cognitive decline, cardiac effects, breathing effects, hormonal effects, addiction, accidental overdose, and death, reflecting a low benefit to risk ratio for long-term opioid therapy.⁷⁶⁰ These risks increase with increasing dose and duration of the drug.⁷⁶¹ Hence, the high risks associated with opioids necessitate a longer study period to assess the true benefit-to-risk ratio for all patients.
- d. A series of reviews, including several in the Cochrane Database, a collection of reviews that summarize the results of medical research, have reached similar conclusions regarding the inadequacy of the scientific evidence of long-term opioid therapy for chronic non-cancer pain.

⁷⁵⁷ Naliboff BD, Wu SM, Schieffer B, *et al.* A randomized trial of 2 prescription strategies for opioid treatment of chronic nonmalignant pain. *J Pain*. 2011;12(2):288-296, at p. 288.

⁷⁵⁸ *Id.* at p. 291.

⁷⁵⁹ *Id.* at p. 295.

⁷⁶⁰ Lembke *et al.*, “Weighing The Risks,” fn.4, above, at p. 985; *see also* Chou, “Effectiveness and Risks”, fn. 308, above, at p. ES-1; *see also* Edelman EJ, Gordon KS, Crothers K, *et al.* Association of Prescribed Opioids with Increased Risk of Community-Acquired Pneumonia among Patients with and Without HIV. *JAMA Internal Medicine*. 2018, at p. 298.

⁷⁶¹ Chou R, Turner JA., Devine EB, *et al.* The Effectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med*. 2015;162(4). doi:10.7326/M14-2559, p. 283.

- i. The 2010 Cochrane Review (Noble 2010) found that there was only “weak” evidence to support the use of opioids for chronic non-cancer pain.⁷⁶²
 - A. “All of the evidence bases considered in this systematic review were of low internal validity and therefore at potentially high risk of bias.” Reasons for this assessment included the funding source (“Only two studies did not clearly have a funding source with a potential conflict of interest in the findings (*e.g.*, drug company),” failure to compare characteristics of dropouts to those of patients who completed the studies, and failure to describe recruitment methods. The highest risk of bias existed for the “continuous outcomes” of pain relief and quality of life, because “high attrition rates affect both the risk of bias and the generalizability of the results from the continuous data outcomes.”⁷⁶³
 - B. At pp. 9-14, specific data on attrition were provided: For the “strong opioid” category (categories described at p. 7), including extended release morphine, controlled release oxycodone, extended release oxymorphone, extended release tramadol and methadone; for oral medications, 34.1% discontinued due to adverse effects⁷⁶⁴ and 10.3% discontinued due to insufficient pain relief,⁷⁶⁵ for a total of 44.4% who discontinued strong oral opioids.⁷⁶⁶ Almost half of all study participants dropped out of the study before it was complete, yet their data was not included in the final analyses.
 - C. The review states that only 273 (58%) of those who began the long-term extensions of short-term trials remained in the study at the 6-7.5 month cut-off point where data were available for all three oral opioid studies. “Because the attrition rate is so high, the participants are likely highly selected, and the data may be biased.”⁷⁶⁷

⁷⁶² Noble M, Treadwell JR, Tregear SJ, *et al.* Long-term opioid management for chronic noncancer pain. *Cochrane Database Syst Rev.* 2010;(1):CD006605. doi:10.1002/14651858.CD006605.pub2, p. 2.

⁷⁶³ *Id.* at pp. 7-8.

⁷⁶⁴ *Id.* at p. 10

⁷⁶⁵ *Id.* at p. 13.

⁷⁶⁶ *Id.* at pp. 9-14.

⁷⁶⁷ *Id.* at p. 15.

- D. The authors report pain relief for those able to remain on oral opioids for six months; however: “The strength of the evidence supporting this conclusion is weak.”⁷⁶⁸
- E. Quality of Life (QoL):
 - I. For oral morphine: A single study (Allan, 2005), reporting a “small improvement on the mental subscale and a larger improvement of the physical subscale” provided an “insufficient quantity of data from which to draw conclusions.”⁷⁶⁹
 - II. QoL improvement was “weakly supported” with transdermal fentanyl (TDF).⁷⁷⁰ For QoL with intrathecal opioids, there were inconsistent findings “No conclusions can be drawn.”⁷⁷¹
- F. “Data describing long-term safety and efficacy of opioids for CNCP [chronic non-cancer pain] are limited in terms of quantity and quality. An evidence base consisting of low-quality studies provides only *weak evidence* from which to draw qualitative conclusions and only low-stability evidence from which to draw quantitative conclusions.” (Emphasis added.)⁷⁷²
- G. “Despite the identification of 26 treatment groups with 4,768 participants, the evidence regarding the effectiveness of long-term therapy in CNCP was too sparse to draw firm conclusions.”⁷⁷³
- ii. Another Cochrane Review of opioids in the treatment of chronic low back pain (CLBP) (Chaparro 2013) found, “There is some evidence (*very low to moderate quality*) for short-term efficacy (for both pain and function) of opioids to treat CLBP compared to placebo.”⁷⁷⁴ (emphasis in original). Yet the authors make clear there is little or no evidence of opioid efficacy long-term.

⁷⁶⁸ *Id.* at p. 16.

⁷⁶⁹ *Id.* at p. 20.

⁷⁷⁰ *Id.* at p. 21.

⁷⁷¹ *Id.* at p. 22.

⁷⁷² *Id.* at p. 23.

⁷⁷³ *Id.* at p. 25.

⁷⁷⁴ Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared to placebo or other treatments for chronic low-back pain. Cochrane Database Syst Rev. 2013. doi:10.1002/14651858.CD004959.pub4, at p. 2

- A. “There are no placebo-RCTs supporting the effectiveness and safety of long-term opioid therapy for treatment of CLBP We have no information from randomized controlled trials supporting the efficacy and safety of opioids used for more than four months. Furthermore, the current literature does not support that opioids are more effective than other groups of analgesics for LBP such as anti-inflammatories or anti-depressants.”⁷⁷⁵
 - B. “The very few trials that compared opioids to non-steroidal anti-inflammatory drugs (NSAIDs) or antidepressants did not show any differences regarding pain and function. The initiation of a trial of opioids for long-term management should be done with extreme caution, especially after a comprehensive assessment of potential risks.”⁷⁷⁶
- iii. Another Cochrane review (McNicol 2013) found: “While intermediate term studies all indicated that opioids were better than placebo, most studies were small, most were short, and none used methods known to be unbiased. All these features are likely to make effects of opioids look better in clinical trials than they are in clinical practice.”⁷⁷⁷ Note that the McNicol review defined “intermediate” term studies as 35-84 days (*i.e.*, 5-12 weeks). Accordingly, these so-called intermediate studies are actually 12 weeks or less, therefore too brief to provide data relevant to efficacy for chronic pain, typically defined as lasting 12 weeks or more.⁷⁷⁸
- iv. Another 2014 Cochrane Review reached similar conclusions: “Similar to previous systematic reviews of randomized trials on opioid therapy for non-cancer pain [cites omitted], we found that most of the trials included in our review had a treatment duration of several days or a few weeks only.”⁷⁷⁹
 - A. “Although some of the newer trials in the update had slightly longer treatment durations [citations omitted], in none of the trials did the participants receive opioids for longer than six months. This is still too short to address the impact of opioid treatment on routine clinical practice in the treatment of a chronic condition

⁷⁷⁵ *Id.*

⁷⁷⁶ *Id.*

⁷⁷⁷ McNicol E, Midbari A, Eisenberg E. Opioids for neuropathic pain (Review). *Cochrane Database Syst Rev.* 2013. doi:10.1002/14651858.CD006146.pub2, at p. 3

⁷⁷⁸ *Id.* at p. 13.

⁷⁷⁹ da Costa BR, Nuesch E, Kasteler R, *et al.* Oral or transdermal opioids for osteoarthritis of the knee or hip *Cochrane Database Syst Rev.* 2014, at p. 28.

such as osteoarthritis. While no evidence of long-term effects is available from randomized trials, observational studies indicate that long-term treatment with opioids of chronic conditions such as osteoarthritis may have deleterious effects and do not seem to improve pain relief [citation omitted].”⁷⁸⁰

- B. Reviewers found that the “small mean benefit” was “contrasted by significant increases in the risk of adverse events. For the pain outcome in particular, observed effects were of questionable clinical relevance since the 95% CI [confidence interval] did not include the minimally clinically important difference” of 0.9 cm on a 10 cm visual analog scale.⁷⁸¹
- C. The 2014 Cochrane Review included studies of tapentadol, as well as several other opioids. In particular, a study of tapentadol by Afilalo, et al., was among the studies as to which the Cochrane Review found too little evidence of benefit to justify the risk.⁷⁸² Afilalo compared tapentadol ER 100-250 mg twice daily against placebo or oxycodone CR 20-50 mg twice daily.⁷⁸³ The primary, pre-specified endpoint of the study was changes from baseline Average Pain Intensity (API) as measured on an 11-point numerical rating scale (NRS).⁷⁸⁴ The Afilalo study was funded by Johnson and Johnson, and 9 of the 10 listed authors were employed by either J&J or Grunenthal (the German entity that developed tapentadol).⁷⁸⁵
- D. To correctly interpret the results of an efficacy study, it is important to distinguish between “statistical significance,” a numerical calculation, and “clinical significance,” which addresses the question of whether a patient experiences a noticeable beneficial difference with the treatment under investigation. Contrary to the practice of setting a pre-specified, “minimal

⁷⁸⁰ *Id.*

⁷⁸¹ *Id.* at p. 2. Some authors have endorsed a “Minimal Important Difference” of 1.0 cm rather than 0.9 cm on the 10 cm VAS. *See e.g.*, Busse JW, Wang L, Kamaleldin M. Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. *JAMA*. 2018;320(23):2448-2460. doi:10.1001/jama.2018.18472. In either case, the salient point is that opioid therapy generally does not meet even this minimal threshold of efficacy in randomized clinical trials, which makes the extraordinary risks of opioid therapy all the more unacceptable.

⁷⁸² da Costa, “Oral or transdermal” fn. 779, above, at p. 15.

⁷⁸³ Afilalo M, *et al.* Efficacy and safety of tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee *Clin. Drug Investig* 2010; 30:489-505.

⁷⁸⁴ Tapentadol (CG5503), Clinical Trials.Gov (last updated Apr. 18, 2012), <https://clinicaltrials.gov/ct2/show/NCT00421928>.

⁷⁸⁵ Afilalo, “Efficacy and Safety”, fn. 783, above, at p. 503.

clinically important difference” by which to assess relevant changes, as described in the Cochrane review (above), the Afilalo study did not establish such a standard. Instead, the authors reported “statistically significant” reduced average pain intensity for tapentadol compared to placebo, although the API difference between tapentadol and placebo was only 0.7 cm,⁷⁸⁶ which fails to meet the test of a minimally clinically important difference. That this study failed to mention the lack of a *clinically* significant difference between tapentadol and placebo for the primary, prespecified endpoint, suggests the possibility of bias in reporting.⁷⁸⁷

- E. In 2015, Janssen and Grunenthal funded a study by Buynak et al purporting to evaluate the long-term efficacy of tapentadol ER among subjects with osteoarthritis or low back pain, who had completed one of four underlying, manufacturer-sponsored studies, one of which was the Afilalo study described above.⁷⁸⁸ The Buynak 2015 article does not state that the underlying studies failed to meet the accepted standard for a Minimally Important Difference from placebo (Afilalo 2010, -0.7 cm; Buynak 2010, -0.8 cm; Lange 2010, -0.6 cm).
- F. As noted in the Cochrane Review (2010), above, the highest risk of bias occurs in opioid studies for the “continuous outcomes” such as pain relief because high attrition rates affect the risk of bias and the generalizability of the results. The tapentadol studies described above suffer from such bias, in that (1) the underlying studies all experienced significant dropout rates (only 57.3%, 52.2%, 56.5% and 46.2% of the tapentadol subjects completed the Afilalo, Buynak 2010, Lange, and Wild studies, respectively); and (2) only 60.5% of the subjects completed the study analyzed in the 2015

⁷⁸⁶ *Id.* at p.489.

⁷⁸⁷ The authors emphasized a claim of “clinical” significance based on a statistically significant result for one of six secondary endpoints, that is, the proportion of subjects reporting more than 50% improvement in pain intensity from baseline. <https://clinicaltrials.gov/ct2/show/NCT00421928>. However, the Afilalo study made no adjustment to impose a more strict test of significance due to testing of multiple endpoints.

⁷⁸⁸ Buynak R *et al.*, Long-term safety and efficacy of tapentadol extended release following up to 2 years of treatment in patients with moderate to severe, chronic pain: results of an open-label extension trial. *Clin. Ther.* 2015; 37:2420-2438. In addition to the Afilalo study, the Buynak (2015) article analyzed data for patients from prior manufacturer-sponsored studies by Buynak R. *et al.* Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo-and active-controlled phase III study. *Expert Opin. Pharmacother.* 2010; 11:1787-1804; Lange B, *et al.*, Efficacy and safety of tapentadol prolonged release for chronic osteoarthritis pain and low back pain. *Adv. Ther* 2010; 27:381-399; Wild JE, *et al.* Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain. *Pain Practice* 2010; 10:416-427. The Wild study did not include a placebo group and thus provided no data regarding difference in average pain intensity between tapentadol and placebo.

Buynak article,⁷⁸⁹ even though the population that entered the latter study consisted of the subset of subjects who had successfully completed the prior trials. In each study, adverse events and lack of efficacy were leading reasons for failure to complete the study.

- v. Chou *et al.* in their 2015 systematic review on the effectiveness of opioids in the treatment of chronic pain stated: “Evidence is *insufficient* to determine the effectiveness of long-term opioid therapy for improving chronic pain and function. Evidence supports a dose-dependent risk for serious harms.”⁷⁹⁰ The authors reported that most placebo-controlled studies were less than 6 weeks, and none were over 16 weeks long. “We did not include uncontrolled studies for these outcomes; reliable conclusions cannot be drawn from such studies because of the lack of non-opioid comparison group and heterogeneity of the results.”⁷⁹¹
- vi. In 2009, Chou was the lead author of a panel made up of a majority of Industry-funded physicians and psychologists who promulgated Guidelines that allowed for the use of chronic opioid therapy; in the same publication, those authors admitted that evidence regarding chronic opioid therapy was “insufficient to assess effects on health outcomes.”⁷⁹²
- In another systematic review of opioid and non-opioid medication for acute or chronic low back pain, Chou *et al.* found that evidence for opioids “remains limited to short term trials showing modest effects versus placebo for chronic low back pain.”⁷⁹³ Shortcomings of the studies included high attrition (30-60% in most trials) and “short follow-up” (one at 16 weeks, all others shorter).⁷⁹⁴ Authors also noted: “Trials were not designed to assess the risk for overdose or opioid use disorder because of relatively small samples, short follow up, and exclusion of higher risk patients; in addition, many studies used an enriched enrollment randomized withdrawal design which could underestimate harms.”⁷⁹⁵ (See paragraphs 6.e, below, for discussion of enriched enrollment study design).

⁷⁸⁹ Buynak, “Long-term safety”, fn. 788, above, at p. 2424.

⁷⁹⁰ Chou. “Effectiveness and Risks -Systematic Review”, fn. 761, above, at p. 276 (emphasis added.)

⁷⁹¹ *Id.* at p. 280.

⁷⁹² Chou, *et al.*, “Clinical Guidelines,” fn.752, above, at p. 130.e5.

⁷⁹³ Chou R, Deyo R, Friedly J, *et al.* Systemic pharmacologic therapies for low back pain: A systematic review for an American College of physicians clinical practice guideline. *Ann Intern Med.* 2017. doi:10.7326/M16-2458, at p. 480.

⁷⁹⁴ *Id.* at p. 483

⁷⁹⁵ *Id.* at pp. 486-487.

- viii. In a systematic review and meta-analysis (Häuser, *Schmerz*, 2015) of open-label continuation trials up to 26 weeks in duration in patients with a variety of different chronic pain disorders, the authors state "... the risk of bias [for these studies] was high ... all studies were funded by the manufacturers of the drugs⁷⁹⁶ average pain scores are unrepresentative of patient experience and of very limited utility⁷⁹⁷ The positive effects of opioid in long-term open-label studies cannot be disentangled from those of co-therapies not controlled for, from unspecific (placebo) effects because of the lack of placebo group or from the spontaneous recovery because of the lack of no treatment group. The external validity of open-label extension studies was comprised [sic] by a highly selected group of patients without major medical disease or mental disorders. The self-selected group of patients who were willing to participate in the open-label extension studies does not permit a clear conclusion on the long-term efficacy of opioids in routine clinical care."⁷⁹⁸
- ix. At a 2001 Janssen Scientific Advisory Board, while discussing how to promote Janssen's fentanyl patch, Duragesic, the consensus statements made it clear that funding for research would be contingent on getting results favorable to Duragesic: "If a pilot pans out we may increase funding to expand the study."⁷⁹⁹ And "The goals for EMRP studies should be explicitly stated: Janssen wants to obtain certain data and seed studies that, after completion, may be expanded by funding from other sources."⁸⁰⁰ This is indicative of the types of bias that can arise from industry-funded studies.
- e. Many studies used an enriched enrollment randomized withdrawal (EERW) study design, an inherently biased methodology which *a priori* favors opioids over placebo. EERW design selects patients who are predisposed to tolerate and prefer opioids, and hence are not reflective of the general clinical population.
 - Randomized, double blind, placebo-controlled trials of 12 weeks durations or less (15 studies total) of opioids in the treatment of chronic pain used to get FDA approval, relied on enriched enrollment design (Meske *et al.* 2018),⁸⁰¹ and hence were biased toward favoring opioids. Open-label

⁷⁹⁶ Häuser W, Bernardy K, Maier C. Long-term opioid therapy in chronic noncancer pain: A systematic review and meta-analysis of efficacy, tolerability and safety in open-label extension trials with study duration of at least 26 weeks. *Schmerz*. 2015. doi:10.1007/s00482-014-1452-0, at p. 4.

⁷⁹⁷ *Id.* at p. 7

⁷⁹⁸ *Id.* at p. 8.

⁷⁹⁹ JAN-MS-00481055 at -1056

⁸⁰⁰ *Id.* at -1057.

⁸⁰¹ Meske DS, Lawal OD, Elder H, Langberg V, Paillard F, Katz N. Efficacy of opioids versus placebo in chronic pain: A systematic review and meta-analysis of enriched enrollment randomized withdrawal trials. *J Pain Res*. 2018. doi:10.2147/JPR.S160255, at pp. 923-934.

continuation trials commonly included subjects who successfully completed the randomized controlled trial phase using an enriched enrollment design. Hence those who entered the open label phase included those who successfully tolerated opioids through the randomized controlled trial period, resulting in an additional layer of bias favoring opioids, and diminishing the applicability of the study results to real world conditions.

- ii. For example, of the 295 initial subjects in the study by Caldwell *et al.* (2002) 222 subjects were assigned to opioid groups and 73 were assigned to placebo.⁸⁰² A 4-week randomized controlled trial (RCT) preceded an open-label phase; 40% of the opioid group who participated in the RCT dropped out due to adverse effects or inadequate pain relief,⁸⁰³ and only those who lasted the full four weeks were permitted to enter the open-label phase. Of the 184 subjects who entered the open-label phase, 131 (72%) came from the opioid groups, while only 50 (28%) came from the placebo group; therefore, the open-label phase included a large majority of subjects who had demonstrated the capability to tolerate opioids, and the study's claims of efficacy are not transferable to a real-world population. Despite the bias favoring opioid-tolerant subjects, more than half failed to complete the open-label phase; 95/181 (52.5%) discontinued.⁸⁰⁴
- iii. A meta-analysis of short term studies (< 6 weeks) confirmed a difference between enriched enrollment studies and non-enriched enrollment studies in terms of adverse medical consequences: "The incidence of adverse effects was noticeably different in the trials that used a classical non-EERW design from those that used the EERW design (Table 3). Among the trials with a non-EERW design, the number of reported adverse effects was 26, while among the trials with an EERW design, only eight adverse effects were reported."⁸⁰⁵
- f. A recent (Busse 2018) meta-analysis confirms that there are no data to show clinically significant long-term efficacy of opioids in the treatment of chronic pain.⁸⁰⁶

⁸⁰² Caldwell JR, Rapoport RJ, Davis JC, *et al.* Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: Results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. *J Pain Symptom Manage.* 2002. doi:10.1016/S0885-3924(02)00383-4, at p. 283.

⁸⁰³ *Id.* at p. 283.

⁸⁰⁴ *Id.* at p. 286.

⁸⁰⁵ Furlan AD, Chaparro LE, Irvin E, Mailis-Gagnon A. A comparison between enriched and nonenriched enrollment randomized withdrawal trials of opioids for chronic noncancer pain. *Pain Res Manag.* 2011;16(5):337-351. doi:10.1155/2011/465281, at p. 347.

⁸⁰⁶ Busse, "Opioids for Chronic Noncancer Pain", fn. 781, above.

- i. The primary study outcomes were “pain relief, physical functioning, and vomiting.”⁸⁰⁷ The study defined the term Minimally Important Difference (MID) as “the smallest amount of improvement in a treatment outcome that patients would recognize as important.”⁸⁰⁸ The data showed that opioid therapy failed to meet the MID as to the primary outcomes of pain relief and physical functioning, as well as the secondary outcomes of emotional functioning, social functioning, or sleep quality compared to placebo.⁸⁰⁹
- ii. For pain relief, the MID was defined as 1 cm on the 10 cm Visual Analog Scale (VAS); the data showed that the difference between opioid therapy and placebo was only 0.79 cm on the VAS, thus no minimally important difference was shown.⁸¹⁰ Despite not meeting the standard, the authors state, “Although the difference did not meet the minimally important difference of 1 cm, opioids were associated with pain relief compared to placebo”⁸¹¹ A more accurate statement would be that opioids were associated with a clinically insignificant difference in pain relief, since the change did not meet the study’s own definition of a clinically significant difference. The study reported a difference of 2.80 favoring opioids over placebo on a 100-point scale for “role functioning;” however, “[w]hen restricted to trials reporting actual change, high quality evidence from 16 RCTs (5329 patients) demonstrated no association of opioids on role functioning compared to placebo.”⁸¹²
- iii. For the primary endpoint of vomiting, the opioid subjects had more than a 4-fold greater risk in nonenrichment trials, and a 2.5 times greater risk in enrichment trials, that is, trials in which subjects were pre-selected for greater ability to tolerate opioid therapy.⁸¹³
- iv. As for “Active Comparator” studies, the authors state: Moderate quality evidence [9 RCTs, 1431 patients] showed “no difference in the association of opioids versus nonsteroidal anti-inflammatory drugs for pain relief,” and the same was true for physical function. The only significant difference was over 4-fold greater vomiting with opioids compared to NSAIDs (RR = 4.74, $p \leq 0.001$).⁸¹⁴

⁸⁰⁷ *Id.* at p. 2449.

⁸⁰⁸ *Id.* at p. 2450.

⁸⁰⁹ *Id.* at pp. 2451, 2455.

⁸¹⁰ *Id.* at p. 2451.

⁸¹¹ *Id.* at pp. 2451-2452.

⁸¹² *Id.* at pp. 2451, 2455.

⁸¹³ *Id.* at p. 2455.

⁸¹⁴ *Id.*

- v. Although the goal was to assess “chronic” non-cancer pain, the authors acknowledge that “it was not possible to assess the long-term associations of opioids with chronic non-cancer pain because no trial followed up patients for longer than 6 months.”⁸¹⁵ There is some inconsistency in the literature about the definition of “chronic.” For example, the Cochrane Review (Noble, 2010) cites the International Association for the Study of Pain (IASP) for a definition of “pain which persists past the normal point of healing,” considered to be 3 months;⁸¹⁶ however, on the very next page, the Cochrane review states that it considered only studies of at least six months, which it termed “Chronic opioid use.”⁸¹⁷ In any case, the Busse authors’ statement that it could not be applied to “long-term” use is an important limitation.
- The Busse study states, “Studies with longer follow-up reported less relief,” which provides significant support for the reduced pain relief of opioids over time, and which buttresses the conclusion that even the minor “improvements” in pain and physical function shown in the studies compiled by Busse, which had a median of only 60 days’ follow-up,⁸¹⁸ cannot be extrapolated to longer term opioid use.
- vii. Over three-quarters of the studies (79%) reported receiving industry funding.⁸¹⁹
- Despite these limitations, the authors concluded: “... some patients may find the modeled proportion of 12% for achieving the minimally important difference for pain relief warrants a trial of treatment with opioids.” The figure of 12% appears to represent the difference between the percentage who reported MID pain relief on placebo (48.7%) and those who reported MID pain relief on opioid therapy (60.6%); difference = 11.9%.⁸²⁰
- ix. In sum, the Busse analysis stands for the proposition that, by submitting to opioid therapy, the patient incurs significant and potentially fatal risks, in exchange for “benefits” that are found to be comparable to placebo for the large majority of subjects studied.
- x. The pain relief MID standard adopted in the Busse study was at the low end of the spectrum of such study definitions, meaning that less improvement was required to meet the MID standard. A pooled analysis of

⁸¹⁵ *Id.* at p. 2457.

⁸¹⁶ Noble, *et al.*, “Long Term Opioid Management,” fn.762, above, at p. 2.

⁸¹⁷ *Id.* at pp. 3, 6.

⁸¹⁸ Busse, *et al.*, “Opioids for Chronic Noncancer Pain,” fn. 781, above, at p. 2451.

⁸¹⁹ *Id.* at p. 2451.

⁸²⁰ *Id.* at p. 2456.

multiple pain studies found that the average MID was 17 mm (1.7 cm) on the VAS scale, or over twice the 0.79 cm difference reported in the Busse meta-analysis.⁸²¹ Despite the lenient standard to show a difference that patients would notice, the Busse results failed that test.

- g. The SPACE randomized clinical trial study, published in JAMA in 2018, comparing opioid and non-opioid medication in the treatment of chronic pain, is the first long-term (one year) randomized controlled trial of opioids in the treatment of moderate to severe pain, and found no benefit of opioids over non-opioid medication.⁸²²
 - i. The SPACE trial showed no benefit of opioids over non-opioid medication (NSAIDs, acetaminophen) in the treatment of moderate to severe chronic back, hip, or knee pain. The opioid group had significantly more adverse medication related symptoms.⁸²³
 - ii. The SPACE trial used a gold standard study design, as follows. It was 12 months in duration, a sufficient length to assess efficacy in the treatment of chronic pain. It included only patients not previously on long-term opioid therapy, and assessed preference for opioids prior to randomization, thereby eliminating the enriched enrollment bias evident in other studies. It used a naturalistic sample of patients in the primary care setting, including some patients with severe depression and post-traumatic stress disorder, the same patients who are often on high dose long-term opioid therapy in real-life.⁸²⁴ Participants were regularly assessed for medication misuse, including checking the prescription drug monitoring database and urine drug testing.⁸²⁵ It was not sponsored by an opioid manufacturer.⁸²⁶
- It is very significant that a gold standard RCT, conducted by independent researchers and published in a leading medical journal (JAMA), reached an opposite result from those claimed by the Pharmaceutical Opioid Industry based on biased, short-term studies conducted by their own employees or paid consultants, and often published in specialty journals. The SPACE trial strongly supports my opinion that chronic opioid therapy

⁸²¹ Olsen MF, Bjerre E, Hansen MD, *et al.* Pain relief that matters to patients: Systematic review of empirical studies assessing the minimum clinically important difference in acute pain. *BMC Med.* 2017. doi:10.1186/s12916-016-0775-3, at p. 10.

⁸²² Krebs EE, Gravelly A, Nugent S, *et al.* Effect of opioid vs non-opioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain the SPACE randomized clinical trial. *JAMA - J Am Med Assoc.* 2018. doi:10.1001/jama.2018.0899.

⁸²³ *Id.* at p. 872.

⁸²⁴ *Id.* at p. 873.

⁸²⁵ *Id.* at p. 875.

⁸²⁶ *Id.* at p. 881.

does not provide greater long-term efficacy, rendering its high risks all the more unacceptable.

- iv. Some patients in the non-opioid group received Tramadol, an opioid, leading to questions about the claim that non-opioids were equally effective. The number of patients receiving Tramadol was small, and Tramadol was administered as a second or third line rescue medicine, to simulate how it might be used in real-life clinical practice. The authors re-ran the data without the patients who were given Tramadol, and the results were “unchanged: over 12 months, pain-related function did not differ between groups ($P=.19$) and the nonopioid group had better pain intensity ($P=.01$).”⁸²⁷ Krebs, *et al.*, also state, “Although both groups improved, we concluded results did not support opioid initiation for chronic back pain or osteoarthritis pain because opioids did not demonstrate any treatment advantages that offset their well-known risks of death and addiction.”⁸²⁸
- h. The opinion has been expressed that a 3-month study is the “standard clinical trial duration accepted by the FDA for many chronic conditions.”⁸²⁹ However, some manufacturers have tested their pain medications in significantly longer randomized clinical trials against other pain relievers. For example, the VIOXX label indicates that VIOXX was tested in clinical trials of up to 86 weeks for osteoarthritis of the knee and hip, against ibuprofen;⁸³⁰ and the CELEBREX label states that CELEBREX was tested in clinical trials of up to 24 weeks in a rheumatoid arthritis population, as well as a 9-month clinical trial that revealed higher rates of complicated ulcers among patients taking CELEBREX plus aspirin for cardiac prophylaxis, compared to CELEBREX alone.⁸³¹ Similarly, manufacturers of opioids could have conducted clinical trials of longer duration; if they had done so, it is likely that the results would have been comparable to those found by Krebs, that is, a higher risk of adverse events and no “treatment advantages” to offset those risks.⁸³² Such early testing would have contradicted the promotion of opioids purported benefits and claims of low risks, which would have discouraged the widespread use of opioids and prevented the ensuing epidemic.
- i. Other studies have also shown that opioids are no better than non-opioids for pain treatment.

⁸²⁷ Krebs EE et al., In reply: opioids vs nonopioids for chronic back, hip or knee pain. *JAMA*. 2018;305(5): 508-509 at p. 509.

⁸²⁸ *Id.*

⁸²⁹ Meske, “Efficacy of opioids versus placebo”, fn. 801, above, at pp. 923-924.

⁸³⁰ Vioxx label (2004), see https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/21647_vioxx_lbl.pdf at p. 3

⁸³¹ Celebrex label (2005), see https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/020998s017lbl.pdf at pp. 4, 6-7

⁸³² Krebs, “In reply”, fn. 827, above, at p. 509.

- i. In the Cochrane Review by Chaparro, *et al.*, discussed above, opioids were not superior to non-opioids for chronic low back pain.⁸³³
- ii. In a review of randomized head to head comparisons of opioids versus non-opioid pain relieving medication, non-opioids were found to be superior to opioids in terms of physical function and tolerability for short term (4-12 weeks) therapy of neuropathic, low back, and osteoarthritic pain.⁸³⁴
- iii. A systematic review comparing oral NSAIDs with opioids for treatment of pain due to knee osteoarthritis over at least 8 weeks' duration found opioids were no better than NSAIDs.⁸³⁵
- j. The evidence for long-term opioid therapy for chronic non-cancer pain, going all the way back to Portenoy's 1986 article,⁸³⁶ was never more than "weak." Such "weak evidence" was never sufficient to justify the Pharmaceutical Opioid Industry's misleading messaging or the significant increase in opioid prescribing for chronic pain. Moreover, the "weak evidence" based on flawed studies of the past has been refuted by strong, gold-standard randomized clinical trial evidence⁸³⁷ that opioids are *not* more effective than non-opioid pain relievers, while imposing greater risk.⁸³⁸ "Weak evidence" of benefit to a small minority of patients was never sufficient to offset the strong evidence of risk. According to the National Academy of Science, Engineering, and Medicine (NASEM) 2017 Report, "Pain Management and the Opioid Epidemic," there is a "*lack of evidence that the drugs are effective for long-term pain management*" (VonKorff *et al.*, 2011) (emphasis added).⁸³⁹
- k. Evidence of the imbalance between significant risk and minimal benefit is reinforced by the studies demonstrating that significant numbers of pain patients will go on to long-term use of these addictive drugs, even with brief opioid exposure. Long-term exposure increases the risk of developing the disease of opioid addiction.

⁸³³ Chaparro, *et al.*, "Opioids Compared to Placebo," fn.774, above, at p. 2.

⁸³⁴ Welsch P, Sommer C, Schiltenswolf M, Häuser W. Opioids in chronic noncancer pain-are opioids superior to non-opioid analgesics? : A systematic review and meta-analysis. *Schmerz*. 2015. doi:10.1007/s00482-014-1436-0, at p. 3.

⁸³⁵ Smith SR, Deshpande BR, Collins JE, Katz JN, Losina E. Comparative pain reduction of oral non-steroidal anti-inflammatory drugs and opioids for knee osteoarthritis: Systematic analytic review. *Osteoarthr Cartil*. 2016. doi:10.1016/j.joca.2016.01.135, at p. 962.

⁸³⁶ Portenoy, Foley, "38 Cases", fn. 186, above.

⁸³⁷ Krebs *et al.*, "Effect of Opioid," fn. 822, above, at p. 873; Welsch *et al.*, "Opioids in Noncancer Pain," fn. 834, above, at p. 3.

⁸³⁸ Krebs *et al.*, "Effect of Opioid," fn. 822, above, at p. 880.

⁸³⁹ NASEM 2017 Report, at fn. 51, above, at p. 29.

- l. The ASPPH Report concluded, “We urge that, consistent with CDC guidelines, opioid pain relievers be treated as highly addictive, controlled substances *not typically indicated for long-term use for chronic pain* outside of active cancer treatment, palliative care, and end-of-life care; and for which lobbying and marketing are inappropriate.”⁸⁴⁰
- m. A recent VA/DoD guideline is even more emphatic, stating, “We recommend *against* initiation of long-term opioid therapy for chronic pain. (Strong against).”⁸⁴¹ The authors stress that “Based on the evidence, it was considered that *opioid therapy should no longer be given when all nonopioid approaches fail due to the substantial risk of harms*. The CDC guideline states, ‘Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patients.’ Our guideline takes a *stronger stance against opioid therapy*, largely driven by the risk for development of opioid use disorder. Both guidelines find little evidence of benefit for long-term opioid use.”⁸⁴²
- n. I have reviewed a letter submitted by the American Medical Association to the CDC on June 16, 2020, advocating major revisions to the CDC 2016 Guidelines for opioid use.⁸⁴³ While this letter asserts that some patients are benefitting from long-term opioid therapy for chronic pain, it provides no data to support that assertion, nor to rebut the great weight of authority cited above. Further, the letter omitted the undisputed body of evidence of OUD and mortality, which would be exacerbated by the absence of the CDC and VA/DoD guidelines to limit dose and duration of opioid therapy. I agree with the AMA letter’s advocacy for a preference for non-pharmacologic and non-opioid therapies; however, the evidence supports the VA/DoD determination that opioids should no longer be given even when other approaches fail, due to the substantial risk of harms. Physicians’ freedom to treat their patients as they choose is not absolute, but must be tempered by evidence and data. AMA’s emphasis on physicians’ freedom is out of proportion to the clear evidence of risk, and the lack of evidence of benefit, for long-term opioid therapy for chronic pain.
- o. Opioids have been generally considered appropriate for cancer pain, because cancer treatment has been closely aligned with end-of-life care, a stage when risks of addiction are considered less important than potential palliative care. However,

⁸⁴⁰ ASPPH Report, “Bringing Science”, fn. 16, above, at p. 11 (emphasis added).

⁸⁴¹ Rosenberg JM, *et al.* Opioid Therapy for Chronic Pain: overview of the 2017 US Department of Veterans Affairs and US Department of Defense clinical practice guidelines. *Pain Medicine*. 2018;19:928-941, at p. 930 (emphasis added).

⁸⁴² *Id.* (emphasis added)

⁸⁴³ James L. Madara, MD (AMA) to Deborah Dowell, MD (CDC), Re: Docket No. CDC-2020-0029, June 16, 2020, <https://searchlf.ama-assn.org/undefined/documentDownload?uri=%2Funstructured%2Fbinary%2Fletter%2FLETTERS%2F2020-6-16-Letter-to-Dowell-re-Opioid-Rx-Guideline.pdf>.

patients with cancer related pain, even at the end of life, are not immune to addiction and they should be monitored carefully for addiction and other adverse consequences, and should receive the lowest dose for the shortest possible duration.

- i. A first-person perspective piece in the *New England Journal of Medicine*, describes the experience of an oncologist (cancer doctor) whose patient gets addicted to opioids.⁸⁴⁴ In my clinical experience, opioid misuse and addiction are as common among cancer patients as non-cancer patients.
- ii. There were more than 15 million cancer survivors in the United States in 2016.⁸⁴⁵ Even patients with cancers once considered incurable, now go into remission for decades and more, emphasizing the need for caution in treating a very large population of patients with opioids.

8. The Pharmaceutical Opioid Industry misrepresented that the risk of addiction to prescription opioids is “rare,” or “less than 1%,” when in fact prescription opioids are as addictive as heroin, and the risk of addiction is far higher than stated by the Industry. The best, conservative data show an opioid addiction prevalence of 10-30% among chronic pain patients prescribed opioids.

- a. Even when being prescribed by a doctor for a legitimate pain condition, opioid painkillers are as addictive as heroin purchased on a street corner, because the prescription opioids have the same addictive effects on the neurocircuitry of the brain.⁸⁴⁶ The addictiveness of prescription opioids has been demonstrated in many studies, yet the Pharmaceutical Opioid Industry has consistently downplayed this risk.
- b. A 2015 systematic review by Vowles, *et al.*, provides the most reliable pooled estimate of the risk of addiction (10-30%) in patients receiving chronic opioid therapy.⁸⁴⁷ The Vowles review is cited by the ASPPH Task Force to state the risk

⁸⁴⁴ Loren AW. Harder to Treat Than Leukemia - Opioid Use Disorder in Survivors of Cancer. *N Engl J Med*. 2018;379(26).

⁸⁴⁵ Bluethmann SM, Mariotto AB, Rowland JH. Anticipating the “silver tsunami”: Prevalence trajectories and comorbidity burden among older cancer survivors in the United States. *Cancer Epidemiol Biomarkers Prev*. 2016. doi:10.1158/1055-9965.EPI-16-0133, at p. 1029.

⁸⁴⁶ See, e.g., Okie S, A flood of opioids, a rising tide of deaths. *NEJM* 2010;363(21): 1981-1985: Prescription opioids are “essentially legal heroin.” (Quoting FDA Advisory Committee member Lewis Nelson. “We need to think about how we would conduct a REMS [Risk Evaluation and Mitigation Strategy] if we were going to be marketing heroin.” at p. 1981.)

⁸⁴⁷ Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, Van Der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: A systematic review and data synthesis. *Pain*. 2015. doi:10.1097/01.j.pain.0000460357.01998 fl. at p. 569. I address the link between prescription opioid addiction and heroin addiction below in §C.9.i.

of addiction and misuse of prescription opioids,⁸⁴⁸ reinforcing my opinion as to the validity of the Vowles review.

- i. Vowles' data synthesis prioritized studies using real world data designed to research opioid misuse and addiction. They also prioritized subjects from real world populations, rather than pre-screened clinical trial subjects enrolled in studies not designed to assess misuse or addiction. The authors adopted *a priori* criteria to assess study quality, and then checked their pooled results against the data from the highest quality studies.⁸⁴⁹ (By contrast, Fishbain *et al.*, described below, completely excluded studies that did not meet their quality standards, which they admitted were arbitrary.) Further, Vowles, *et al.* disclosed that they had no conflicts of interest.⁸⁵⁰ Because most available studies used patient questionnaires rather than objective urine drug screening, Vowles' analysis would represent a likely underestimate of addiction, despite a more appropriate selection of real world populations for the study.
- ii. In their systematic review and meta-analysis from 38 studies, Vowles, *et al.* cite a wide range of problematic prescription opioid use in patients being treated for a medical condition, ranging from <1% to 81% across studies. Across most calculations, rates of opioid misuse averaged between 21% and 29% (range, 95% confidence interval [CI]: 13%-38%), and rates of opioid addiction averaged between 8% and 12% (range, 95% CI: 3%-17%).⁸⁵¹
- iii. Even the lower risk classification of 8-12% would be considered a "very common" risk according to the World Health Organization and the Council of International Organizations of Medical Sciences:⁸⁵²
 - A. Very common $\geq 1/10$
 - B. Common $\geq 1/100$ and $< 1/10$
 - C. Uncommon $\geq 1/1000$ and $< 1/100$
 - D. Rare $\geq 1/10,000$ and $< 1/1,000$

⁸⁴⁸ ASPPH Report, "Bringing Science", fn. 16, above, at p. 14.

⁸⁴⁹ Vowles, "Rates of Opioid Misuse", fn. 847, above, at p. 570-571.

⁸⁵⁰ *Id.*, at p. 575.

⁸⁵¹ *Id.* at, pp. 572-573. It is noteworthy that well-respected scientific sources have cited Vowles' article as a reliable estimate of risk. See, e.g., Els, *et al.*, High-dose opioids for chronic non-cancer pain: an overview of Cochrane Reviews. *Cochrane Database Syst Rev.* 2017 Oct; 2017(10): CD012299, citing the Vowles article as support for "rates of addiction averaging between 8% and 12%.

⁸⁵² World Health Organization, CIOMS, http://www.who.int/medicines/areas/quality_safety/safety_efficacy/trainingcourses/definitions.pdf, at p. 10.

- E. Very rare < 1/10,000
- F. Although the US has not adopted a standard hierarchy like WHO/CIOMS, frequency of adverse events in product information material in the United States is consistent with the WHO standards: “rare” in US labels is commonly < 1/1000; “Infrequent” is >1/1,000 to < 1/100; and anything over 1/100 is “frequent.”⁸⁵³
- iv. Vowles’ definition of “misuse” as culled from the included articles is consistent with the DSM-5 definition of mild opioid use disorder.⁸⁵⁴ As such, the prevalence of opioid use disorder in Vowles’ review using DSM-5 criteria is between 21-29%, including the spectrum from mild through severe OUD.⁸⁵⁵ (This is reasonably consistent with the Boscarino, *et al.* study⁸⁵⁶ described below.)
- v. As with other meta-analyses, reports of misuse/addiction were higher in studies which relied on urine drug testing instead of self-report. For example, included in the Vowles analysis, a study by Brown, *et al.* demonstrated the lower rates based on self-report versus those based on urine toxicology.⁸⁵⁷
 - A. This was a nonrandomized, open-label study of morphine sulfate ER (Avinza) for a titration period of 2-4 weeks followed by treatment for 12 weeks, administered to patients in primary care settings, evaluated for risk stratification and aberrant behaviors (including urine screening, early renewal requests, increased dose without authorization, oversedation).⁸⁵⁸
 - B. Only 561 (38%) of the 1,570 originally enrolled patients completed the study, despite its relatively brief duration of 12 weeks of treatment. Of the 890 patients for whom reasons for withdrawal were provided, 410 (46%) included adverse events or failure of treatment among their reasons to withdraw. Five percent were

⁸⁵³ Eriksson R, Aagaard L, Jensen LJ, *et al.* Discrepancies in listed adverse drug reactions in pharmaceutical product information supplied by the regulatory authorities in Denmark and the USA. *Pharmacol Res Perspect.* 2014;2(3):1-10. doi:10.1002/prp2.38, at p. 6.

⁸⁵⁴ Vowles, “Rates of Opioid Misuse”, fn. 847, above, at p. 574.

⁸⁵⁵ *Id.* at p. 569.

⁸⁵⁶ Boscarino J, Rukstalis MR, Hoffman SN, *et al.* Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 vs. DSM-4 diagnostic criteria. *J Addict Dis.* 2011;30(3):185-194. doi:10.1080/10550887.2011.581961.

⁸⁵⁷ Brown J, Setnik B, Lee K, *et al.* Assessment, stratification, and monitoring of the risk for prescription opioid misuse and abuse in the primary care setting. *J. Opioid Management.* 2011;(December):467-483 doi:10.5055/jom.2011.0088.

⁸⁵⁸ *Id.* at p. 468.

asked to withdraw due to investigator assessment of “high risk level for drug abuse/misuse” after enrollment, and another 5% for “noncompliance.”⁸⁵⁹

- C. The Vowles analysis incorporates the Brown study’s assertion that 2-3% of patients exhibited aberrant drug-related behaviors during visits 2 through 4, and 6% at visit 5, listing those percentages in the “misuse” column.⁸⁶⁰
- D. However, Urine Drug Screening (UDS) showed much higher rates of misuse and/or addictive use (although Vowles did not include these findings in the analysis): In particular, 17, 11, 11 and 15 subjects had positive UDS for oxycodone in weeks 2-5, despite prohibition of that drug after Visit 1.⁸⁶¹ By week 5, there were 79 subjects remaining in the study, and the 15 subjects with positive UDS for oxycodone yield a rate of 19% misuse and/or addictive use. This finding provides objective evidence that the prevalence of aberrant drug-related behavior was approximately 3 to 9 times the “2-6%” rate of aberrant drug related behaviors reported by the investigators⁸⁶² and cited by Vowles. Such use occurred despite patients having signed agreements to refrain from illicit drug use, and despite knowledge that UDS would be conducted.⁸⁶³
- E. Objective measures of addictive/aberrant behavior like drug screening results are more reliable than questionnaire responses, and these data from the Brown study support that view.
- F. This study was Pfizer-sponsored. Authors included Pfizer/subsidiaries/consultants.⁸⁶⁴
- vi. Also included in the Vowles analysis was a study by Fleming, *et al.*, again highlighting the discrepancy between self-report and urine toxicology.⁸⁶⁵
 - A. This Fleming article reported on substance use disorders among 801 chronic pain patients receiving daily opioid therapy from the same Wisconsin primary care practices that provided the

⁸⁵⁹ *Id.* at p. 473.

⁸⁶⁰ *Id.* at p. 572.

⁸⁶¹ *Id.* at p. 475, Figure 2.

⁸⁶² *Id.* at p. 476.

⁸⁶³ *Id.* at pp. 478-479.

⁸⁶⁴ *Id.* at p. 481.

⁸⁶⁵ Fleming MF, Balousek SL, Klessig CL, Mundt MP, Brown DD. Substance Use Disorders in a Primary Care Sample Receiving Daily Opioid Therapy. *J Pain*. 2007. doi:10.1016/j.jpaa.2012.02.008, at p. 579.

population analyzed in the Fleming article discussed above. Fleming reported a point prevalence of 3.8% for opioid use disorder and 9.7% for substance abuse and/or dependence, using DSM-4 criteria⁸⁶⁶ and Vowles incorporated these percentages into the data synthesis.

- B. The diagnoses included in the percentages above were based on a 2-hour interview of each patient by the doctor or nurse at the primary care practice.⁸⁶⁷ As referenced above, Fleming noted the large disparity between the patients' self-reporting of other drug use and the results of urine drug screening. There were 156 positive urine screens for cannabis compared to 106 self-reports, and 60 positive urine screens for cocaine compared to 24 self-reports.⁸⁶⁸
- C. Although the article provided urine drug screen data on certain illicit drugs, sufficient to show the discrepancy between deceptive self-report and objective toxicology, the article did not provide data on the results of urine screens specifically for opioids, so there were no data to determine how many patients used opioids that were not prescribed (evidence of misuse), or less/no evidence of the prescribed opioids (evidence of possible diversion).
- D. Fleming also reported that "the frequency of opioid use disorders was 4 times higher in patients receiving opioid therapy compared with general population samples (3.8% vs 0.9%)."⁸⁶⁹
- E. Despite acknowledging the disparity between toxicology tests and diagnoses based on interview data, Fleming concluded that the "3.8% rate of opioid addiction is a small risk compared with the alternative of continuous pain and suffering. The data presented in this paper support the use of opioids for the treatment of chronic pain by primary care physicians."⁸⁷⁰ I disagree with this interpretation of the findings, especially in light of (a) the acknowledged disparity between the urine drug screen rate and the rate based on self-reports; (b) the unreliability of the latter; and (c) the unwarranted assumption that opioid therapy would alleviate chronic pain and suffering as a trade-off for accepting the risk of dependence or addiction.

⁸⁶⁶ *Id.* at p. 573.

⁸⁶⁷ *Id.* at p. 574.

⁸⁶⁸ *Id.* at p. 579.

⁸⁶⁹ Fleming, *et al.*, "Substance Use Disorders," fn. 865, above, at p. 573.

⁸⁷⁰ *Id.* at p. 581.

- c. A study indicating a high risk of addiction from prescription opioids was published by Boscarino, *et al.*, who analyzed addiction rates in a large population of patients receiving opioids to treat a medical condition, and found a 41.3% lifetime prevalence of opioid use disorder (using DSM-5 criteria).⁸⁷¹ The research in this study is strengthened by the fact that it was based on a random sample of outpatients seen in a large multispecialty group practice. Subjects were identified through drug orders in the electronic health records and subsequently were interviewed using the final DSM-5 criteria. Weaknesses include the low numbers willing to be interviewed (33%).⁸⁷²
- i. “Using electronic records from a large US health care system, we identified outpatients receiving five or more prescription orders for opioid therapy in the past 12 months for noncancer pain (mean prescription orders =10.72; standard deviation =4.96). In 2008, we completed diagnostic interviews with 705 of these patients using the DSM-4 criteria. In the current study, we reassessed these results using the final DSM-5 criteria. Results: The lifetime prevalence of DSM-5 opioid-use disorders using the final DSM-5 criteria was 58.7% for no or few symptoms (<2), 28.1% for mild symptoms (2–3), 9.7% for moderate symptoms (4–5), and 3.5% for severe symptoms (six or more). Thus, the lifetime prevalence of “any” prescription opioid-use disorder in this cohort was 41.3% (95% confidence interval [CI] =37.6–45.0).”⁸⁷³
- ii. “A comparison to the DSM-4 criteria indicated that the majority of patients with lifetime DSM-4 opioid dependence were now classified as having mild opioid-use disorder, based on the DSM-5 criteria (53.6%; 95% CI =44.1–62.8). In ordinal logistic regression predicting no/few, mild, moderate, and severe opioid-use disorder, the best predictors were age 65 years, current pain impairment, trouble sleeping, suicidal thoughts, anxiety disorders, illicit drug use, and history of substance abuse treatment.”⁸⁷⁴
- iii. In my opinion, the moderate-severe categories of DSM-5 OUD are consistent with Vowles’ definitions of addiction, and the milder DSM-5 diagnoses are more consistent with Vowles’ definition of misuse.⁸⁷⁵ Accordingly, the totals of 13% “moderate to severe opioid use disorder” in Boscarino are consistent with Vowles’ findings of 8-12% “addicted”;

⁸⁷¹ Boscarino J, Hoffman S, Han J. Opioid-use disorder among patients on long-term opioid therapy: impact of final DSM-5 diagnostic criteria on prevalence and correlates. *Subst. Abuse Rehabil.* 2015;83. doi:10.2147/SAR.S85667, at p. 83.

⁸⁷² *Id.* at p. 84.

⁸⁷³ *Id.* at p. 83.

⁸⁷⁴ *Id.* at p. 83.

⁸⁷⁵ Vowles, “Rates of Opioid Misuse”, fn. 847, above, at p. 574.

further, Vowles' finding of 21-29% "misuse" is reasonably consistent with Boscarino's report of 28% with "mild opioid use disorder." In other words, both of these publications are reasonably consistent in assessing the risk of opioid addiction, ranging from mild to severe, in a clinical population of patients receiving opioids.

- d. Even very limited exposure to prescription opioids can result in addiction, as evidenced by a study in teens and young adults: 14,888 persons aged 16 to 25 years-old who received an initial opioid prescription from a dentist, found that 6% were diagnosed with an opioid use disorder (OUD) within one year. For women in this group, the rate was 10%. This study highlights the risk to teens and young adults, even after limited exposure to a dental procedure, such as removal of wisdom teeth.⁸⁷⁶
- e. A 2019 study found that for opioid-naïve individuals receiving an initial opioid prescription between 2011-2014, "long-term opioid use (3+ months) is associated with more than double the risk of incident OUD and opioid-related death."⁸⁷⁷ In fact, the cumulative incidence of opioid use disorder rose for each time period measured after opioid naïve individuals received an opioid prescription, so that for those receiving an initial opioid prescription in 2011, the cumulative incidence of OUD was 0.62% at 6 months, 1.18% at 1 year, 2.244% at 2 years, 3.79% at 3 years and 4.90% at 4 years.⁸⁷⁸
- f. Numerous other publications have reported addiction rates from prescription opioids higher than those that appear in the Pharmaceutical Opioid Industry promotional materials that I have reviewed. These include the following prevalence studies cited in the Vowles⁸⁷⁹ data synthesis: Manchikanti (2003),⁸⁸⁰ Cowan (2003),⁸⁸¹ Adams (2006),⁸⁸² Fleming (2007),⁸⁸³ Banta-Green (2009),⁸⁸⁴

⁸⁷⁶ Schroeder AR, Dehghan M, Newman TB, Bentley JP, Park KT. Association of Opioid Prescriptions From Dental Clinicians for US Adolescents and Young Adults With Subsequent Opioid Use and Abuse. *JAMA Intern Med.* 2018, at p. E6.

⁸⁷⁷ Burke LG, et al. Trends in opioid use disorder and overdose among opioid-naïve individuals receiving an opioid prescription in Massachusetts from 2011 to 2014. *Addiction.* 2019;1-12, at p. 9

⁸⁷⁸ *Id.*, p. 6, Table 3

⁸⁷⁹ Vowles, *et al.*, "Rates of Opioid Misuse," fn. 847, above.

⁸⁸⁰ Manchikanti, *et.al* Prevalence of prescription drug abuse and dependency in patients with chronic pain in western Kentucky. *J Ky Med Assoc* 2003;101:511-17, at p. 511.

⁸⁸¹ Cowan DT, Wilson-Barnett J, Griffiths P, Allan LG. A survey of chronic noncancer pain patients prescribed opioid analgesics. *Pain Med.* 2003;4(4):340-351, at p. 340.

⁸⁸² Adams EH, Breiner S, Cicero TJ, *et al.* A Comparison of the Abuse Liability of Tramadol, NSAIDs, and Hydrocodone in Patients with Chronic Pain. *J Pain Symptom Manage.* 2006;31(5):465-476, at p. 465.

⁸⁸³ Fleming, *et al.*, "Substance Use Disorders," fn.865, above, at p. 573.

⁸⁸⁴ Banta-Green CJ, Merrill JO, Doyle SR, Boudreau DM, Calsyn D a. Opioid use behaviors, mental health and pain--development of a typology of chronic pain patients. *Drug Alcohol Depend.* 2009;104(1-2):34-42, at p. 37.

Schneider (2009),⁸⁸⁵ Edlund (2007),⁸⁸⁶ Hojsted (2010),⁸⁸⁷ Jamison (2010),⁸⁸⁸ Passik (2011),⁸⁸⁹ and Meltzer (2012),⁸⁹⁰ which reported addiction at 8.4%, 2.8%, 4.9%, 3.8%, 13%, 15.7%, 0.7%, 14.4-19.3%, 34.1%, 6-11%, and 23%, respectively. With one exception, all of these studies showed addiction prevalence multiple times higher than the “less than one percent” figure that Defendants continued to cite, while omitting data from these peer-reviewed studies of relevant, real world populations of chronic opioid patients.⁸⁹¹

⁸⁸⁵ Schneider, MD, PhD JP, Kirsh, PhD KL. Defining clinical issues around tolerance, hyperalgesia, and addiction: A quantitative and qualitative outcome study of long-term opioid dosing in a chronic pain practice. *J Opioid Manag.* 2010;6(6):385-395, at p. 390.

⁸⁸⁶ Edlund MJ, Sullivan M, Steffick D, Harris KM, Wells KB. Do users of regularly prescribed opioids have higher rates of substance use problems than nonusers? *Pain Med.* 2007. doi:10.1111/j.1526-4637.2006.00200.x, at p. 651.

⁸⁸⁷ Højsted J, Nielsen PR, Guldstrand SK, Frich L, Sjøgren P. Classification and identification of opioid addiction in chronic pain patients. *Eur J Pain.* 2010;14(10):1014-1020, at p. 1014.

⁸⁸⁸ Jamison RN, Butler SF, Budman SH, Edwards RR, Wasan AD. Gender Differences in Risk Factors for Aberrant Prescription Opioid Use. *J Pain.* 2010. doi:10.1016/j.jpain.2009.07.016, at p. 5.

⁸⁸⁹ Passik SD, Messina J, Golsorkhi A, Xie F. Aberrant drug-related behavior observed during clinical studies involving patients taking chronic opioid therapy for persistent pain and fentanyl buccal tablet for breakthrough pain. *J Pain Symptom Manage.* 2011;41(1):116-125, at p. 116.

⁸⁹⁰ Meltzer, E, Rybin, D, *et al.* Aberrant Drug-Related Behaviors: Unsystematic Documentation Does Not Identify Prescription Drug Use Disorder. *Pain Med.* 2012 November; 13(11): 1436-1443, at p. 1437.

⁸⁹¹ The sole exception, the Edlund (2007) study, can be explained in that the 0.7% incidence pertained to the entire healthcare database, rather than the subset of prescription opioid users. As to the latter group, the incidence of addiction was actually 7.3%, which is consistent with the other data synthesized by Vowles. Edlund MJ, *et al.*, Do Users of Regularly Prescribed Opioids Have Higher Rates of Substance Use Problems Than Nonusers? *Pain Medicine.* 2007; 8(8):647-656, at p. 651. Because this distinction is important and not obvious, I provide the additional details below.

First, the data used in the Edlund 2007 study came from a nationally representative community sample, Healthcare for Communities (HCC). The sample consisted of 9,279 people who were interviewed to investigate self-reported opioid misuse and “problem” opioid misuse among users and non-users of prescribed opioids, as well as use/ “problem use” of other substances (illicit drugs other than opioids, alcohol). “Opioid misuse” was defined to mean either without a doctor’s prescription, or in a larger amount or for a longer time than prescribed. “Problem opioid use” added criteria of tolerance and/or psychological or emotional problems due to drug use to the general “misuse” definition. *Id.* at pp. 649-650.

This Edlund study did not provide any data on “addiction.” Nevertheless, the Vowles data synthesis included a value of 0.7% for “addiction.” Vowles, *et al.*, “Rates of Opioid Misuse,” fn. 847, above, at p. 572, Table 2. However, the Edlund definition of “problem opioid use” is consistent with Vowles’ definition of “addiction” to mean a “[p]attern of continued use with experience of, or demonstrated potential for, harm, (e.g., impaired control over drug use, compulsive use, continued use despite harm, and craving).” *Id.* at p. 570.

Further, the reference to “0.7%” in the Edlund 2007 article appearing at p. 651, stated the percentage of problem opioid misuse in “*the total HCC sample,*” (emphasis added), which consisted of 8,997 (97%) nonusers of prescription opioids compared to 282 (3%) of the HCC sample who were prescription opioid users. The Edlund study reported, “Rates of problem opioid misuse were *significantly higher in those with prescription opioid use* (7.3%, 17 out of 282, vs. 0.5%, 69 out of 8,997, P<0.001.”; (emphasis added)). Edlund, *et al.*, “Do Users Have Higher Rates,” fn. 891, above, at p. 651.

In the absence of any data specific to addiction in the Edlund article, it can only be inferred that Vowles intended to use Edlund’s “problem opioid misuse” as a surrogate for addiction, and that the reference to 0.7% for the total population is inappropriate, since all of the other studies that Vowles synthesized had determined the

Footnote continued on next page

- g. The above-described studies show that pain treatment with opioids is naturally linked with addiction. Furthermore, this linkage would have been known and obvious to Defendants before and throughout the period of time when they marketed and promoted their opioid medications with the false message that addiction was “less than 1%,” or “rare,” or “uncommon,” and that false message deprived doctors and patients of necessary data to inform the true risks of chronic opioid therapy. Internal documents show that Defendants were aware of the link between prescription opioids and opioid misuse, diversion, addiction and death, as discussed below.
- i. On April 22, 2011, Joseph Tomkiewicz, Corporate Investigator at AmerisourceBergen, sent an email to colleagues under the subject “Saw This and Had To Share It ...”⁸⁹² It was a parody written to the tune of the Beverly Hillbillies: “Come and listen to a story about a man named Jed, A poor mountaineer, barely kept his habit fed.... Said Sunny Florida is the place you ought to be, So they loaded up the truck and drove speedily, South, that is, Pain Clinics, cash ‘n carry, A Bevy of Pillbillies Pill Mills that is. Buy some pills. Take a load home.”⁸⁹³ This is shocking for its gross disregard of human suffering caused by the opioid epidemic. Just as shocking is the fact that the offensive email was circulated among several high-ranking regulatory affairs executives and diversion control investigators at Amerisource Bergen, who not only failed to express disapproval, but rather stated, “I sent this to you a month or so ago--nice to see it recirculated,” with a “smiley face” icon.⁸⁹⁴

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percentage of addiction/ misuse among subjects exposed to prescription opioids, and not the percentage of addiction/misuse among a general population consisting almost entirely of non-users of prescription opioids.

Thus, the proper figure from the Edlund study to include in the Vowles data synthesis would have been “7.3%, 17 out of 282” prescription opioid users, and the inclusion of the prescription opioid nonusers differentiates the Edlund study from all others that Vowles used in his data synthesis. At 7.3%, the Edlund study is very similar to the range of 8-12% addiction that Vowles assessed for the studies as a whole.

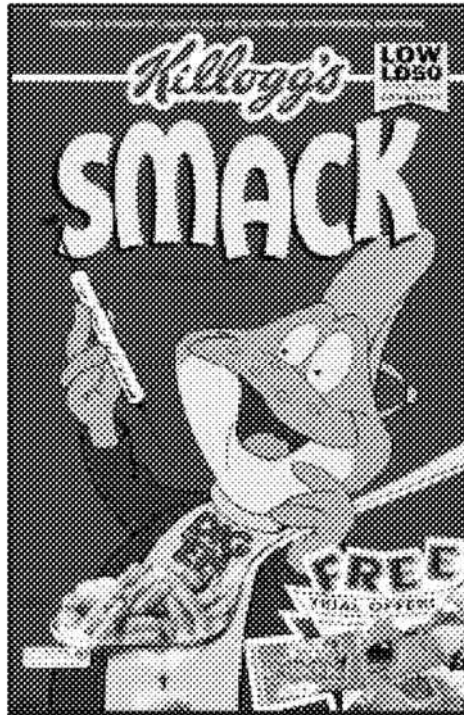
Finally, Edlund acknowledged, “Our analyses of substance abuse rely on self-report, which might suffer from recall bias, or respondents might under-report symptoms due to the stigma associated with illicit substance abuse. To the extent this is true, our results are underestimates of the true rates.” *Id.* at p. 654. Accordingly, 7.3% is a lower bound, and the true rate of addiction among the population in the Edlund study may well have been greater.

⁸⁹² ABDCMDL05795672

⁸⁹³ *Id.*

⁸⁹⁴ *Id.* The email’s recipients included Julie Eddy (Director State Government Affairs) Chris Zimmerman (Vice President Corporate Security and Regulatory Affairs), Edward Hazewski (Director Diversion Control Program) , Kevin Kreutzer (Diversion Control Investigator), David Breitmayer (Diversion Control Investigator), Paul Ross (Senior Director Corporate Security Regulatory Affairs), Bruce Gundy (Director of Investigations) , Robert Crow (Director Security Services), and Steve Mays (Senior Director Corporate Security and Regulatory Affairs - Group Compliance Officer, Drug Distribution). See <https://www.linkedin.com/in/julie-eddy-458b118>, <https://www.linkedin.com/in/chriszimmerman>, <https://www.linkedin.com/in/edwardhazewski>, <https://www.linkedin.com/in/kevin-kreutzer-b1763512>, <https://www.linkedin.com/in/davebreitmayer>, <https://www.linkedin.com/in/abdcmdl05775790>, <https://www.linkedin.com/in/bruce-gundy-5b5085a>, <https://www.linkedin.com/in/robert-crow-7b97aa192>, <https://www.linkedin.com/in/steve-mays-47833336>.

- ii. On July 2, 2012, the same AmerisourceBergen employee, Joseph Tomkiewicz, also sent to colleagues under the subject “Oxycontin for kids”, an image resembling a Kellogg’s cereal box, but instead of “Kellogg’s” it reads “Killogg’s”, the cereal is called “SMACK”, a slang term for heroin, and the cereal box features a frog with a syringe getting ready to inject, holding up a spoonful of pills, next to a bowl of coupons labeled “Free Trial Offer” as shown below.⁸⁹⁵



- iii. This image encapsulates the link between prescription opioids, industry promotion of those opioids through marketing strategies like coupons for free samples, and the development of opioid addiction which in some cases leads to illicit opioids like heroin. As in the case of the “Pillbillies” email, the “Smack” email was circulated among several employees without evidence of any objections.⁸⁹⁶
- iv. On June 19, 2015, a memorandum from Healthcare Distribution Management Association (HDMA) titled “Strategy to Turn the Tide in West Virginia,” summarizes suggestions for distributors to fend off

⁸⁹⁵ ABDCMDL00532594

⁸⁹⁶ *Id.* The email’s recipients included Kevin Kreutzer (Diversion Control Investigator), David Breitmayer (Diversion Control Investigator), Edward Hazewski (Director Diversion Control Program), and Elizabeth Garcia (Corporate Investigator). See <https://www.linkedin.com/in/kevin-kreutzer-b1763512>, <https://www.linkedin.com/in/davebreitmayer>, <https://www.linkedin.com/in/edwardhazewski>, ABDCMDL00532649.

negative press and lawsuits due to their role in inciting the opioid epidemic.⁸⁹⁷ This memorandum includes the statement, “The fact is that 200 million pills over a four-year period is a significant problem. The story is made worse given the following: The distributors do not want to make their sales data public.... While patient access issues can help support the need for distributors, they can also turn against distributors, as these companies must self-monitor and restrict the supply of medicine to protect their ability to continue serving the needs of doctors, pharmacists, and their patients.”⁸⁹⁸ HDMA is an alliance of pharmaceutical distributors, largely funded by the Defendants in this litigation.⁸⁹⁹

- v. In a 2001 discussion regarding abuse reports relating to Duragesic, Janssen’s VP of Pain, Steve Zollo stated, “let’s be clear about this issue – As the use of Duragesic continues to rise (which it will), so will drug abusers trying to find creative ways to extract fentanyl from the patch. That’s why it’s a scheduled drug. As our use goes up, so will published reports of abuse.”⁹⁰⁰ Yet in a 2001 Duragesic patient guide, Janssen made false and misleading statements regarding the addictive potential of Duragesic, stating that “addiction is relatively rare when patients take opioids appropriately.”⁹⁰¹
- vi. In 2001, Janssen convened an advisory board to discuss the Duragesic patch. When the topic of Duragesic’s addictive potential was raised, advisory board members, who were all KOLs in the field of pain, had this to say:
 - A. “All opioids are in the same class and have the same potential for abuse.”⁹⁰²
 - B. “So why is OxyContin so subject to abuse? ... Availability - \$1B worth on the market. Street price indicates likelihood of diversion.”⁹⁰³
 - C. “Drug abusers will figure out how to abuse Duragesic once it is more available As market share goes up, so will abuse. Over-

⁸⁹⁷ ABDCMDL00269293

⁸⁹⁸ *Id.*

⁸⁹⁹ Healthcare Distribution Alliance (formerly known as the HDMA) leadership remains with David Neu of AmerisourceBergen, <https://www.hda.org/persons/david-neu>

⁹⁰⁰ JAN-MS-00287030 at -7031.

⁹⁰¹ JAN-MS-02757826 at -7847.

⁹⁰² JAN-MS-00481055 at -1059.

⁹⁰³ *Id.*

promising on the lack of abuseability is what got OxyContin in trouble. Duragesic should not repeat the same mistake.”⁹⁰⁴

- D. These comments make it clear that members of the advisory board were well aware of the risks of misuse, addiction, and overdose deaths caused by prescription opioids, and that these risks were directly tied to availability, which increases the risk of patients getting addicted, and also diversion to non-patients. Despite the KOLs advice, Janssen promoted Duragesic in ways similar to those that “got OxyContin in trouble,”⁹⁰⁵ including free samples and aggressive marketing of purported low risk of addiction (See 5.a.ii for discussion of Duragesic free samples and promotion) .
- h. Opioid manufacturers have sought to counter evidence of addiction risk by claiming ‘abuse-deterrent’ status for their products. For example, Janssen sought FDA approval of an “abuse deterrence” claim for tapentadol (Nucynta). However, an FDA Memorandum in 2008 noted that tapentadol displayed “high abuse potential comparable to that of hydromorphone, a drug that is associated with high levels of abuse.”⁹⁰⁶ The FDA authors likened tapentadol to “other strong opioids such as hydromorphone and oxycodone,” and warned against using tapentadol IR “chronically as this increases the adverse event profile, including the likelihood of addiction and abuse.”⁹⁰⁷ Further, the memorandum noted that tapentadol causes dependence and subjective withdrawal on par with oxycodone.⁹⁰⁸
- i. A study by Butler *et al.* in *Pain Medicine* (2015), sponsored by Janssen, reports on a population of about 114,000 patients evaluated for prevalence and prescription-adjusted prevalence of self-reported, past 30-day “abuse” of tapentadol in comparison to several other opioids, between January 2011 and September 2012.⁹⁰⁹ Tapentadol IR “abuse” prevalence was reported to be lower than all other opioids except fentanyl, while tapentadol ER “abuse” prevalence was reported to be lower than other opioids except hydromorphone.⁹¹⁰ (Of interest, 20.8% of the population

⁹⁰⁴ *Id.* at 1060.

⁹⁰⁵ *Id.*

⁹⁰⁶ Food and Drug Administration Center for Drug Evaluation and Research (FDA-CDER), Application Number: 22-304 (November 4, 2008), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022304s000_OtherR.pdf, at p. 2. The relatively lower rates of misuse and diversion of tapentadol formulations in the community to date are likely a function of lower prescribing rates, a shorter period since the drug was approved for sale, and lower level awareness of the drug among prescribers, patient consumers, and individuals with opioid addiction, not an intrinsically lower abuse potential of tapentadol.

⁹⁰⁷ *Id.* at p. 3.

⁹⁰⁸ *Id.* at p. 9.

⁹⁰⁹ Butler SF *et al.* Tapentadol Abuse Potential: a postmarketing evaluation using a sample of individuals evaluated for substance abuse treatment. *Pain Medicine*. 2015;16: 119-130, at p. 119.

⁹¹⁰ *Id.*

self-reported “abuse” of analgesics within the last 30 days.)⁹¹¹ Most importantly, rate of “abuse” adjusted for number of prescriptions⁹¹² (tapentadol had far fewer prescriptions than other opioids), demonstrates that tapentadol “abuse” was greater than tramadol and nearly identical to hydrocodone. It is likely that tapentadol, with a similar “abuse potential” to hydrocodone, would show similar rates of addiction and diversion if prescribed at equal volumes.

- ii. A study by Cepeda *et al.* (2013), also Janssen-funded, reported a 65% lower rate of “abuse” in a relatively small cohort of 6,000 total tapentadol subjects compared to 37,000 oxycodone subjects, identified in 2010 and followed for one year.⁹¹³ However, the study provided no details as to the duration of exposure to either drug. Since duration of exposure is a significant cause of opioid use disorder, the absence of such data weakens the validity of the findings. Also, there are significant differences in prescribing rates between tapentadol and oxycodone, with much higher prescribing for oxycodone. Comparing these two drugs fails to take into account the longer history on the market and greater drug awareness for oxycodone. This is further supported by the animal and human studies finding tapentadol comparable to morphine, hydromorphone, and oxycodone in its likeability, reinforcing properties, and propensity for physiologic dependence, as noted in the 2008 FDA memorandum referenced above.⁹¹⁴
- iii. For the same reasons, a drug diversion surveillance study by Dart *et al.*, which finds relatively low rates of tapentadol diversion, is not a good measure of problematic opioid use in the community.⁹¹⁵ Lower rates of tapentadol diversion are likely attributable to lower tapentadol prescribing rates and the ready availability of other opioids in the community. This opinion is supported by FDA reviewers, who stated in a 2013 letter to Janssen that in regard to tapentadol “abuse” in the community, “it is unclear whether the relatively low amount of abuse detected is due to a low level of awareness of the drug as a consequence of its short marketing history, low utilization, reduced opioid receptor affinity of the tapentadol molecule, or the tamper-resistant characteristics of the extended-release formulation.”⁹¹⁶

⁹¹¹ *Id.* at p. 122.

⁹¹² *Id.* at p. 119.

⁹¹³ Cepeda, MS *et al.* Comparison of the risks of opioid abuse or dependence between tapentadol and oxycodone: results from a cohort study. *Journal of Pain*. 2013;14(10): 1227-1241 at p. 1227.

⁹¹⁴ FDA-CDER, “22-304”. fn. 906, above, at pp. 8-10.

⁹¹⁵ Dart RC, *et al.* Assessment of the abuse of tapentadol immediate release: the first 24 months. *Journal of Opioid Management* 2012; 8:395-402.

⁹¹⁶ FDA-CDER Letter to Janssen (August 1, 2003). JAN-MS-00704213 at -4219.

- i. Tramadol is an addictive opioid yet was marketed as a “non-narcotic.”
 - i. After ingestion, tramadol is metabolized by the cytochrome P450 2D6 liver enzyme into an active metabolite that binds the opioid receptors and exhibits the same properties as other opioids, like morphine. J&J was well aware of tramadol’s opioid status before marketing it to the public and was specifically instructed not to market tramadol as non-scheduled, i.e. non-addictive, given its robust activity at the opioid receptor.⁹¹⁷ Despite knowledge of tramadol’s potent activity at the opioid receptor, and despite a direct warning from the FDA, as shown below J&J falsely marketed tramadol as “non-narcotic” and repeatedly called attention to its unscheduled status, thus misleading prescribers into thinking tramadol is safer than other opioids and carries less risk of addiction.
 - ii. The 1995 tramadol New Drug Application (NDA) makes it clear that manufacturers knew from before tramadol was marketed that the mechanism of action is that of an opioid. The original labeling for ULTRAM (tramadol) stated, “ULTRAM’s opioid activity derives from low affinity binding of the parent compound to u-opioid receptors and higher affinity binding of the M-1 metabolite....,” and the NDA Review of PharmacologyToxicology Data stated, “This metabolite [M1] appears to play a major role in the opioid binding and analgesic effects, 4 times to nearly 200 times as potent as the parent tramadol and is often present at equivalent blood levels.”⁹¹⁸
 - iii. In a letter from the FDA to the manufacturers dated March 3, 1995, manufacturers were warned not to call attention to tramadol’s (Ultram’s) status as a non-scheduled, i.e. non-addictive drug: “As Ultram may have an abuse potential of an unknown degree, you are not permitted to advertise, promote or market the drug product by calling attention to its unscheduled status under the U.S. Controlled Substance Act.”⁹¹⁹
 - iv. In a 2008 internal J&J document, under “Strengths (Prioritized)”, is the statement: “Ultram ER [tramadol extended release] is non-narcotic which mid-level practitioners can prescribe.”⁹²⁰ The reference to mid-level practitioners implies that tramadol is safer than “narcotics” i.e. opioids, and hence can be prescribed by nurse practitioners who have less training in the risks of pharmacotherapy.
 - v. The “Ultram ER Core Visual Aid Tour” depicts tramadol (Ultram ER) as a safer stepping-stone in a “pain treatment ladder” between non-opioid

⁹¹⁷ FDA-CDER. NDA 20-281 File. (March 3, 1995).

https://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/020281Orig1s000rev.pdf..

⁹¹⁸ *Id.*, at pp. 8, 332.

⁹¹⁹ *Id.* at p. 5.

⁹²⁰ JAN-TX-00022608, produced natively at *2.

medications like acetaminophen/NSAIDs and “scheduled narcotics.” See “Key Points – PAIN LADDER: Use ULTRAM ER before moving to scheduled narcotics to treat moderate chronic pain; Around the clock pain deserves around the clock treatment without the concerns of scheduled narcotics.”⁹²¹ Although it is accurate that tramadol was not scheduled before 2014, this pain treatment ladder is misleading because it suggests that tramadol is not an opioid, and that tramadol is safer than opioids, neither of which is true.

- vi. Tramadol sales representatives were coached to say the following to prescribers while showing them pictures from a direct-to-consumer television ad for Ultram ER, of people looking healthy and happy while engaged in different physical activities - hiking, playing on the beach, climbing stairs: “Doctor, after seeing this commercial, your patients may come to you asking about treatment options, including those that work around the clock. Those patients with chronic low back or osteoarthritis pain may be especially interested. Let’s discuss such a challenging patient in your practice – maybe you have a 50 year old female with chronic OA pain who needs to treat her pain on a daily basis and isn’t getting sufficient pain relief from her prescription NSAIDs, but whom you would rather not move to a scheduled narcotic. For that patient, why not put her on ULTRAM ER before moving her to a scheduled narcotic?”⁹²² (“Ultram ER Core Visual Aid Tour”) The suggestion here is that Ultram ER is somehow less risky than other opioids because it was not “scheduled.” There is no evidence to support this suggestion and substantial evidence to the contrary.
- vii. Tramadol is addictive, as demonstrated by the references below.
- viii. In recognition of its addictive potential, in 2014 tramadol was changed from a non-scheduled drug, to a scheduled drug (Schedule IV).⁹²³
- ix. A study of treatment-seeking adolescents at a substance use treatment facility in Sweden showed “tramadol was by far the most prevalent opioid detected.”⁹²⁴
- x. A study of long-term use of tramadol following acute exposure, published in the British Medical Journal (BMJ 2019,) states: “Our study suggests that tramadol carries a similar or somewhat greater risk of transitioning from acute to prolonged use compared with other short acting opioids.

⁹²¹ JAN-TX-00001492, produced natively at *9.

⁹²² *Id.*, at *7

⁹²³ Schedules of Controlled Substances: Placement of Tramadol into Schedule IV. 79 Fed. Reg. 37,628 (July 2, 2014).at p. 37628

⁹²⁴ Olsson MO, *et al.* High rates of tramadol use among treatment-seeking adolescents in Malmo, Sweden: a study of hair analysis of nonmedical prescription opioid use. *Journal of Addiction* 2015:1-9, at p. 1.

Although prescribing was relatively infrequent (4% of patients with opioid fills, including those who received tramadol with other short acting opioids), tramadol was the third most frequently prescribed opioid in this study (after hydrocodone and short acting oxycodone), and its use seems to be increasing (fig 1).⁹²⁵ The authors conclude, “Our findings suggest that from the standpoint of risk of dependency, clinicians prescribing tramadol for acute pain should exercise a level of caution similar to that surrounding the prescribing of other short acting opioids, including those on higher Drug Enforcement Administration schedules.”⁹²⁶

- A. Persistent medical use of opioids is a risk factor for addictive use. Short-term tramadol prescribing leads to persistent use, especially as doses increase. Thiels reported that receipt of tramadol alone was associated with a 6% increase in the risk of additional opioid use relative to other short-acting opioids; a 47% increase in the risk of persistent opioid use (defined as episodes of use lasting 90 or more days, that started in the 180 days following surgery); and a 41% increase in the most stringent category of persistent use (the CONSORT criteria; opioid use lasting at least 90 calendar days and including either 10 or more opioid fills or 120 or more days supply); all of these increases met criteria for statistical significance.⁹²⁷ Thiels also reported that doses of 300 MME and larger were associated with higher risk of prolonged use (odds ratios 1.1 to 1.6).⁹²⁸ This aligns with CDC data supporting the conclusion that the risk of prolonged use increases significantly when patients receive prescriptions for more opioids.⁹²⁹
- B. Tramadol manufacturers coached sales representatives to push higher doses: “Key Points: 100 mg is only starting dose for most patients – will likely need to go to 200 or 300 mg. Sample Detail: ‘So if we go back to that 50 year old female patient with chronic OA pain, for whom scheduled narcotics are inappropriate does it make sense to prescribe ULTRAM ER and use it on a daily basis to provide effective pain relief? Good. There are three strengths – 100, 200 and 300mg. For patients not already on tramadol, you want to start on 100mg, increasing the dose by 100mg increments

⁹²⁵ Thiels CA, *et al.* Chronic use of tramadol after acute pain episode: cohort study. *BMJ* 2019;365: |1849, 1-10 at pp. 5-6.

⁹²⁶ *Id.* at p. 6.

⁹²⁷ *Id.*, at p. 1.

⁹²⁸ *Id.*, at p. 6.

⁹²⁹ Shah A, Hayes CJ, Martin BC. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use — United States, 2006–2015. *MMWR Morb Mortal Wkly Rep* 2017;66:265–269

every 5 days. The 100 mg dose is just a starting dose for most patients.”⁹³⁰

- xi. Lay press articles have detailed widespread tramadol misuse, addiction, and diversion abroad. For example, a 2015 article reported that tramadol was “ubiquitous” in Egypt, and a clinic physician stated that up to 40% of his patients were “addicted” to tramadol.⁹³¹ Another tramadol article reported that “Fueled by cut-rate Indian exports and inaction by world narcotics regulators, tramadol dependency extends across Africa, the Middle East and into parts of Asia and eastern Europe.”⁹³² The same article reported that, in the U.S., emergency room visits related to tramadol had tripled between 2005-2011, and that, in Northern Ireland, “tramadol is killing more people than heroin.”⁹³³ These sources provide additional support for the conclusion that tramadol is an addictive and dangerous drug.
- xii. The misleading message that tramadol is a “non-narcotic” penetrated the medical literature, including government reports and peer reviewed clinical studies, creating a false sense of safety about tramadol.
 - A. In a September 2011 Government Accountability Office Report to Congressional Requesters on the problem of ‘doctor shopping’, tramadol is listed in Table 1 as a “non narcotic painkiller.”⁹³⁴
 - B. Yet within the report tramadol is among the most common drugs that patients engaged in ‘doctor shopping’ to obtain, fifth behind hydrocodone, oxycodone, morphine, and fentanyl, in a list of fourteen highly addictive prescription drugs.⁹³⁵
 - C. J&J’s own published studies included misleading claims based on tramadol’s non-scheduled status. For example, a 2007 study by Ortho-McNeil Janssen employees stated, “Concerns about regulatory scrutiny can cause the underprescription of conventional opioids and subsequent unrelieved or undermanaged pain. Thus, tramadol may be an option to postpone the use of conventional opioids while providing effective pain relief.”⁹³⁶ This statement is misleading in that it differentiates between tramadol and

⁹³⁰ JAN-TX-00001492, produced natively at *12.

⁹³¹ *Drug Abuse in Egypt: A pill for work and play*, The Economist, April 18, 2015.

⁹³² Justin Scheck, *Tramadol: The opioid crisis for the rest of the world*, Wall St. J., Oct. 19, 2016.

⁹³³ *Id.*

⁹³⁴ US. Government Accountability Office. (2011, September). Medicare Part D: Instances of questionable access to prescription drugs, (Publication No. GAO-11-699,) <https://www.gao.gov/new.items/d11699.pdf>, at p. 11.

⁹³⁵ *Id.*, at Table 2, p. 12.

⁹³⁶ Vorsanger G, *et al.*, Post hoc analysis of a randomized, double-blind placebo-controlled efficacy and tolerability study of tramadol extended release for the treatment of osteoarthritis pain in geriatric patients. *Clin Ther* 2007; 29:2520-2535, at p. 2530.

“conventional opioids,” when in fact tramadol’s mechanism of action includes the M1 metabolite that acts in the same manner as a “conventional opioid,” and it promotes such use on the basis that “regulatory concerns” would thereby be avoided – a coded reference to the tramadol’s non-scheduled status, which J&J had been instructed not to use in its promotion of the drug.⁹³⁷

- xiii. I personally experienced the marketing message that tramadol was not an opioid and was therefore safer and less addictive than opioid pain medications. It is my opinion that my experience was not unique, and that similar or identical messages were conveyed to the medical community in general. Tramadol prescribing went up between 2009 and 2017, even as prescribing of other opioids went down.⁹³⁸ With growing national awareness of the opioid epidemic, J&J promoted tramadol as a ‘safer alternative’, despite evidence of abuse, addiction, and risk of other serious side effects.
 - A. As tramadol prescribing went up, so did reports of harm, including addiction and death, as described below.
 - B. An independent Steering Committee tasked with monitoring tramadol after it went on the market found multiple reports of severe opioid withdrawal following tramadol (Ultram) cessation. Further, in some cases patients were exhibiting symptoms of withdrawal “not normally observed in opiate withdrawal, such as hallucinations, paranoia, extreme anxiety, panic attacks, confusion and unusual sensory experiences such as numbness and tingling in one or more extremities. Withdrawal symptoms of either type were one of the more prevalent adverse events associated with chronic Ultram use, comprising nearly 40% of all adverse events reported with Ultram. Most of these consisted of typical opiate withdrawal symptoms, but 1 in 8 cases presented as atypical. These results indicate that physicians and other healthcare professionals need to be aware of the potential of Ultram to induce withdrawal of the classical opioid type, and that atypical withdrawal may also occur.”⁹³⁹
 - C. A study from the United Kingdom showed prevalence of tramadol users increased from 2000 to 2015, and then significantly reduced after tramadol was made a Schedule IV drug (2014). “Both annual

⁹³⁷ FDA-CDER. NDA 20-281 File. (March 3, 1995).

https://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/020281Orig1s000rev.pdf.

⁹³⁸ Thiels, “Chronic Use of Tramadol”, fn. 925, above, at Figure 1.

⁹³⁹ Senay EC, *et al.* Physican dependence on Ultram (tramadol hydrochloride): both opioid-like and atypical withdrawal symptoms occur. *Drug and Alcohol Dependence* 2003;69:233-241, at p. 233.

tramadol utilisation and rate of tramadol-related deaths increased before tramadol classification and decreased thereafter.”⁹⁴⁰

- D. A 2010 study analyzed tramadol poisoning data from 2003-2009 in the States of West Virginia, Ohio, Kentucky and Arkansas. In 2007-08, Kentucky and Arkansas imposed Schedule IV status on tramadol (several years before the FDA acted to do so), while tramadol remained unscheduled in West Virginia and Ohio.⁹⁴¹ The study showed that poisonings due to tramadol rose in West Virginia and Ohio throughout the study period, while tramadol poisonings rose in Kentucky and Arkansas only until Schedule IV status was imposed, and declined thereafter.⁹⁴² This study period was contemporaneous with the publication of the Vorsanger article promoting the use of tramadol as an alternative to “scheduled” opioids.
- j. In addition to being falsely marketed as non-narcotic and safer/less addictive than other opioids, tramadol was also falsely marketed as safer than non-opioid pain medications like acetaminophen and ibuprofen.
 - i. From Ultram ER Core Visual Aid Tour: “Sample Detail: ‘ULTRAM ER gives you added confidence due to its safety profile. As you know from your experience with tramadol, ULTRAM ER is not a scheduled product and is not associated with the GI or CV warnings of NSAIDs or COX-2s, and ULTRAM ER can be used safely for long term therapy. Please make sure you are familiar with this important Safety Information before you prescribe ULTRAM ER.’”⁹⁴³
 - ii. Because of tramadol’s unique metabolism and mechanism of action, it poses additional risks that do not occur with standard non-opioid medications like acetaminophen and ibuprofen.
- A. The enormous inter-individual variability in CYP2D6 metabolism means that tramadol imposes risks on some patients that are greater than the risks for others, because the degree of metabolism in a given individual is unpredictable and unknown prior to the patient’s experience of an adverse event. Poor metabolizers won’t get sufficient analgesic effects of tramadol, and thus can be left

⁹⁴⁰ Chen T-C, *et al.* A 15-year overview of increasing tramadol utilization and associated mortality and the impact of tramadol classification in the United Kingdom. *Pharmacoepidemiol Drug Saf.* 2018;27:487-494, at p. 487.

⁹⁴¹ Spiller HA, *et al.* Effect of scheduling tramadol as a controlled substance on poison center exposures to tramadol. *Annals of Pharmacotherapy* 2010;44:1016-1021, at p 1017

⁹⁴² *Id.*, at pp. 1018, 1020.

⁹⁴³ JAN-TX-00001492, produced natively at *10

without pain relief. Rapid metabolizers will effectively get more opioids, making them more vulnerable to toxicity.⁹⁴⁴

- B. Case reports of pediatric patients with overactive CYP2D6 enzymes dying from tramadol have been reported. “These ultra-rapid metabolizers experience an increase in the production of active metabolites of codeine and tramadol, which can lead to oversedation, respiratory depression, and death.”⁹⁴⁵ As a result, in 2017, the U.S. Food and Drug Administration updated their warnings regarding tramadol use, making tramadol contraindicated in patients under 12 years of age.⁹⁴⁶
- C. Further, administering tramadol with other medications increases the unpredictability of its metabolism. “Comedication may compromise drug safety by increasing the risk of drug interactions and adverse events, a fact often underestimated in patients. Comedication can produce enzyme induction or inhibition mimicking genetic defects, which also contributes to the variable response to drugs.”⁹⁴⁷
- iii. Tramadol carries the additional risk of seizures⁹⁴⁸ and life-threatening hypoglycemia.⁹⁴⁹ These are not risks typically seen with other analgesics, opioids and non-opioids alike.
- iv. Zeng *et al.* found: “Among patients aged 50 years and older with osteoarthritis, initial prescription of tramadol was associated with a significantly higher rate of mortality over 1 year of follow-up compared with commonly prescribed nonsteroidal anti-inflammatory drugs, but not compared with codeine.”⁹⁵⁰
- k. The Pharmaceutical Opioid Industry has relied on flawed and industry-influenced studies regarding the risk of addiction from prescription opioids. The studies relied on by Defendants to estimate the risk of addiction from prescription opioids provide a significant underestimation of the true risk of misuse, dependence, and addiction for several reasons:

⁹⁴⁴ Stamer UM, *et al.* Concentrations of tramadol and O-desmethytramadol enantiomers in different CYP2D6 genotypes. *Clinical Pharmacology & Therapeutics* 2007;82(1):41-47.

⁹⁴⁵ Fortenberry M, *et al.* The use of codeine and tramadol in the pediatric populations – what is the verdict now? *J Pediatr Health Care* 2019;33:117-123, at p. 117

⁹⁴⁶ *Id.*

⁹⁴⁷ Stamer, “Concentrations of tramadol”, fn. 944, above, at p. 45.

⁹⁴⁸ Ryan NE, Isbister GK. Tramadol overdose causes seizures and respiratory depression but serotonin toxicity appears unlikely. *Clinical Toxicology* 2015;53:545-550, at p. 545.

⁹⁴⁹ Fournier J-P, *et al.* Tramadol use and the risk of hospitalization for hypoglycemia in patients with noncancer pain. *JAMA Intern Med.* 2015;175(2):186-193, at p. 186.

⁹⁵⁰ Zeng C, *et al.* Association of tramadol with all-cause mortality among patients with osteoarthritis. *JAMA* 2019;321(10):969-982, at p. 969.

- i. Many studies, particularly trials conducted by opioid manufacturers, screen out patients at higher risk of addiction, who are not commonly screened from real world clinical exposure.
- ii. Many studies are not designed *a priori* to identify addiction outcomes, which means that they lack methodology to diagnose or otherwise accurately account for the cases.
- Many studies are sponsored and/or written by industry authors, raising conflict of interest and bias issues.
- iv. Many studies are too short to assess addiction risk (as discussed previously).
- v. Many studies do not use rigorous detection methods.
 - A. Most studies rely solely on patient questionnaire responses to identify problematic behavior, despite generally accepted knowledge that a significant subset of respondents will not disclose behaviors of interest that could subject them to stigma, sanction, or both, as exemplified by the Fleming study (discussed above, and below).
 - B. A retrospective study of urine toxicology information for 122 patients maintained on chronic opioid therapy, found that 43% of patients had a “problem” with opioids: positive urine toxicology or one or more aberrant drug taking behaviors. The authors concluded “Monitoring both urine toxicology and behavioral issues captured more patients with inappropriate drug-taking behavior than either alone. Requiring a report of behavioral issues and urine toxicology screens for patients receiving chronic opioids creates a more comprehensive monitoring system than either alone.”⁹⁵¹
 - C. Urine drug tests provide more reliable evidence of drug misuse and addiction than patient report. Fleming found a 24% rate of positive toxicology tests for illicit drugs. “Eighty-four of 185 (46%) patients with positive toxicology testing denied illicit drug use during the research interview, even when they were guaranteed anonymity. This finding confirms clinical observations that patients with chronic pain often mislead their physicians about illicit drug use Minimization of drug use and drug problems by patients is a major concern in all studies that try to estimate rates of addiction, especially for illegal drugs.”⁹⁵² In other words,

⁹⁵¹ Katz NP, Sherburne S, Beach M, *et al.* Behavioral monitoring and urine toxicology testing in patients receiving long-term opioid therapy. *Anesth. Analg.* 2003. doi:10.1213/01.ANE.0000080159.83342.B5, at p. 1097.

⁹⁵² Fleming, *et al.* “Substance Use Disorders,” fn. 865, above, at pp. 580-581.

rates of opioid use disorder were potentially 8 times higher in the same population when objective measures of urine drug screens were used.

- D. Databases with information on prescribing of controlled substances provide more reliable evidence of drug misuse and addiction than patient report. Checking a database with access to this information gives more reliable evidence on duplicate prescriptions, early refills, “doctor shopping,” and other indicators of misuse and addiction.⁹⁵³
- I. A particularly flawed article is the 2008 review by Fishbain, which claimed that the risk of addiction from chronic use of prescription opioids is 3.27% overall; 0.19% if considering de novo opioid users only.⁹⁵⁴ Overall, Fishbain included 67 studies in his review and analysis of various measures of addiction or abuse. With respect to the 3.27% / 0.19% addiction rates, Fishbain stated that he relied on a subset of 24 studies with a total of 82 addiction cases among 2,507 patients, identified in Appendix 1 to the article, accessed at the journal website. However, review of the Appendix 1 table shows only 23 studies with 81 addiction cases among 2173 patients, resulting in a prevalence of 3.73%, rather than 3.27%. These figures are not reliable indicators of true prevalence of OUD, for the reasons explained below.
 - i. The Fishbain analysis included studies that (a) were too short to accurately assess addiction risk; (b) administered low doses; (c) screened out patients at higher risk of addiction; (d) were not designed to identify addiction; (e) did not apply rigorous detection methods; and (f) were sponsored and/or written by industry authors, raising conflict of interest and bias issues.
 - ii. Fishbain’s pooled analysis found substantially higher evidence of drug misuse/addiction (14.5%) when findings were based on the more objective measure of aberrant urine toxicology screens.⁹⁵⁵
 - iii. Fishbain’s 2008 review omitted two studies from his 1992 review that had reported substantially higher prevalence than the pooled figure of 3.27% stated in the 2008 article. Studies by Evans, *Anesthesia* 1981; 36:597-602,⁹⁵⁶ (reported 16% addiction in Fishbain’s 1992 article⁹⁵⁷), and Katon,

⁹⁵³ Centers for Disease Control and Prevention, What States Need to Know about PDMPs. <https://www.cdc.gov/drugoverdose/pdmp/states.html>.

⁹⁵⁴ Fishbain DA, Cole B, Lewis J, Rosomoff HL, Rosomoff RS. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? a structured evidence-based review. *Pain Med.* 2008; 9(4):444-459. doi:10.1111/j.1526-4637.2007.00370.x, at p. 444.

⁹⁵⁵ *Id.* at p. 450.

⁹⁵⁶ Evans PJD. Narcotic addiction in patients with chronic pain. *Anaesthesia.* 1981;36(6):597-602. doi:10.1111/j.1365-2044.1981.tb10323.x.

Am J Psychiatry 1985; 142:1156-60, (reporting 18.9% addiction),⁹⁵⁸ both appeared in Fishbain 1992 but were omitted from Fishbain 2008. Further, the Evans study, in turn, cited to an article by Maruta, *Mayo Clinic Proceedings* 1976; 54:241-4,⁹⁵⁹ which reported an incidence of 24% addiction among a chronic pain population.⁹⁶⁰ Fishbain 2008 stated that his search for relevant articles went back to 1966, so these three references would have been within the time period he searched. Fishbain was a litigation consultant for Defendant Purdue between at least 2005-2008, a relationship that was not disclosed in the 2008 article, and which casts the exclusion of the higher prevalence studies in a disturbing light.

- iv. In 1992, Fishbain had published an earlier study of addiction risk with chronic opioid exposure, which stated, “According to the results of this review, to date, only three studies have attempted to address the concepts of psychological dependence and compulsive use, *i.e.*, addiction, in an acceptable fashion. These studies have found a prevalence from 3.2% to a high of 16% for the possibility of addiction in chronic pain patients.”⁹⁶¹ The same article also stated, “It is interesting to note that the only two studies to utilize urine toxicologies found illicit drug use in 6.41 and 12.5% of their chronic pain patients. These results may therefore indirectly support the results of the other ‘addiction’ studies described earlier, as they are both within the prevalence percentages derived from these studies.”⁹⁶² However, these higher prevalence figures, and the sources from which they came, were omitted from Fishbain’s 2008 analysis.
- Also, Fishbain’s 2008 review⁹⁶³ included data from a 1992 study by Bouckoms, *et al.*, which found that 14 of 59 clinic patients (24%) taking

Footnote continued from previous page

⁹⁵⁷ The Evans article states that the addiction rate was 7%, which appears to be based on 9 cases among the full study population of 130 subjects. (Evans at p. 600) Fishbain’s 1992 article states, “Of 56 chronic *benign* patients, 9 or 16% exhibited features of addiction.” (Fishbain 1992, Table 4, at p. 83; emphasis added). Thus, comparing the two articles, it appears that Evans included the 74 cancer patients, who had no reported cases of addictive behavior, in the total of 130 subjects. Conversely, Fishbain 1992 limited his study to “Drug Abuse, Dependence, and Addiction in *Chronic Pain Patients*,” (emphasis added); thus the figure of 16% (9/56) appears accurate.

⁹⁵⁸ Egan K, Katon W. Chronic Pain: Lifetime Psychiatric Diagnoses and Family History. *Am J Psychiatry*. 1985;(October):1156-1160, at p. 1157.

⁹⁵⁹ Note that the Maruta article was actually published in 1979, and the cite in the Evans article lists the incorrect year of publication.

⁹⁶⁰ Maruta T., Swanson D., Finlayson, R. Drug Abuse and Dependence in Patients with Chronic Pain. *Mayo Clin. Proc.* 1979 (April):241-244, at p. 242.

⁹⁶¹ Fishbain DA, Rosomoff HL, Rosomoff RS. Drug abuse, dependence, and addiction in chronic pain patients. *Clin J Pain*. 1992. doi:10.1097/00002508-199206000-00003, at p. 80.

⁹⁶² *Id.* at p. 81.

⁹⁶³ Fishbain, *et al.*, “What Percentage,” fn. 954, above.

opioids for long-term met criteria for “narcotics addiction.”⁹⁶⁴ Bouckoms also stated: “The influence of population sample bias in prevalence studies of narcotic addiction is dramatically shown in a comparison of studies in the literature. Table 5 summarizes data from the studies of Porter, Maruta, Taub, Evans, Langemark, and Portenoy, wherein the prevalence of addiction was 0.03%, 24%, 4.2%, 7%, 35%, and 5%, respectively.”⁹⁶⁵ Notably, the 0.03% figure in Bouckoms’ text is based on the Porter and Jick 1980 Letter⁹⁶⁶ – the only one of the 5 references that was *not* based on a population of patients treated with opioids for chronic pain.

- vi. All of the sources cited by Bouckoms were available to Defendants from 1992 on. Yet their promotional statements beginning in the 1990s cited the inapt Porter and Jick study⁹⁶⁷ of hospitalized patients with any exposure to opioids, regardless of duration, as the source for the claim of “less than one percent” prevalence of addiction. I am not aware of any Defendants having issued a promotional statement citing the results of 24%, 4.2%, 7%, 35% or 5%, referenced by Bouckoms in 1992.⁹⁶⁸ Nor am I aware of any such statements by Defendants that cited the range of “prevalence from 3.2% to a high of 16% for the possibility of addiction” reported by Fishbain in 1992.⁹⁶⁹ The timeline below shows the dates of publications demonstrating far greater risks of addiction to prescription opioids than those misrepresented by Defendants. Further, the timeline below illustrates that risks were known and published in the peer-reviewed literature well before the 1990s, when the Pharmaceutical Opioid Industry began their misleading marketing of addiction rates that were “less than 1%,” “rare,” “nonexistent,” or “negligible” (see references at §7.b above):

⁹⁶⁴ Bouckoms AJ, Masand P, Murray GB, Cassem EH, Stern TA, Tesar GE. Chronic nonmalignant pain treated with long-term oral narcotic analgesics. *Ann Clin Psychiatry*. 1992. doi:10.3109/10401239209149570, at p. 185.

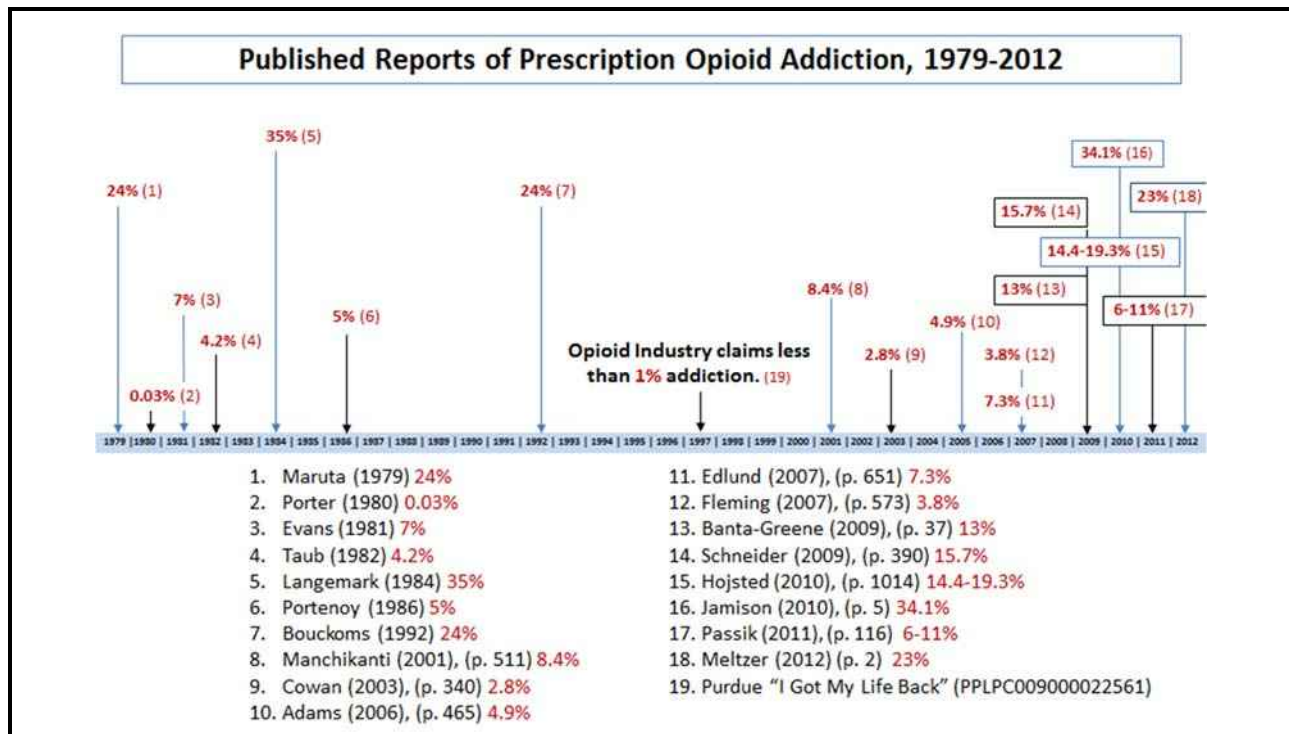
⁹⁶⁵ *Id.* at p. 188.

⁹⁶⁶ Porter, Jick, *et al.*, “Addiction Rare,” fn. 168, above, at p. 123.

⁹⁶⁷ *Id.*

⁹⁶⁸ Bouckoms, *et al.*, “Chronic Nonmalignant,” fn. 964, above, at p. 188.

⁹⁶⁹ Fishbain, *et al.*, “Drug Abuse,” fn. 961, above, at p. 80.



vii. Fishbain made an admittedly “arbitrary” decision to apply a 65% “quality score” requirement, despite his own reference to a source stating that studies with scores below 50% are generally not used.⁹⁷⁰ The Tables in the Appendix to the Fishbain 2008 article provide the quality scores only for the studies that were included, but not for those that were excluded, so it cannot be determined whether the three higher prevalence studies were excluded for failure to meet the arbitrary quality score threshold, or for other reasons. Their absence from the 2008 review casts further doubt on its reliability.

m. Another flawed and biased study that was reviewed by Fishbain was co-authored by Portenoy.⁹⁷¹ In this study, 27 physicians who attended training sessions to serve on “a pain-oriented speakers’ bureau” applied a “Pain Assessment and Documentation Tool” (PADT) to 388 of their patients, with diverse pain syndromes, who had been on various regimens of chronic opioid therapy for at least 3 months.⁹⁷² The physicians reported their assessment that 5.93% (23/388) of their patients were addicted.⁹⁷³ However, the doctors also reported that 19.3 % (75/388) engaged in 3 or more “aberrant drug-taking behaviors,” such as requests

⁹⁷⁰ Fishbain, *et al.*, “What Percentage,” fn.954, above, at p. 448.

⁹⁷¹ Passik SD, Kirsh KL, Whitcomb L, *et al.* Monitoring outcomes during long-term opioid therapy for noncancer pain: Results with the Pain Assessment and Documentation Tool. *J Opioid Manag.* 2005.

⁹⁷² *Id.* at p. 258.

⁹⁷³ *Id.* at p. 263.

for early renewals, increasing doses without authorization, reporting lost or stolen prescriptions, obtaining medications from other doctors, declining physical/social/psychological function, over-sedation, etc.; and that 10.8% (41/388) engaged in 5 or more such behaviors.⁹⁷⁴ Their conclusion of 5.93% addicted lacks validity for several reasons.

- i. Appendix 1 states: “Of the total sample 5.93% were thought to demonstrate opioid prescription abuse/addition [sic].”⁹⁷⁵ This is not correct, since the 5.93% applies solely to addiction, whereas the abuse rates were much higher, as described above.
 - ii. Other studies on Fishbain’s reference lists would count such behaviors as evidence of addiction, such that the addiction rate in the Passik study would be about 2 to 4 times greater than the 5.93% rate based on the doctors’ reports. Including the full range of opioid use disorder (mild, moderate, severe) based on DSM-5 criteria, this study’s summative results (5.93% + 19.3% + 10.8%) demonstrate that 36.06% of patients met DSM-5 criteria for opioid use disorder, approximating the 40% rate of opioid use disorder consistent with the Boscarino, *et al.* study⁹⁷⁶ described above.
 - iii. The possibility of underestimating the addiction rate is of particular concern in light of the participating physicians’ roles as Speakers’ Bureau trainees.
- n. In yet another flawed study reviewed by Fishbain *et al.*, 10 patients, who had been treated for chronic noncancer pain (CNCP) with morphine for an average of 2 years, participated in a study alternating between one 60 hour period of morphine and one 60 hour period of placebo (two and a half days each).⁹⁷⁷ “When asked ‘Do you have any drug craving?’ (graded as mild, moderate or severe), no patients reported craving for morphine or a compulsion to take any,” during the period of cessation of opioids.⁹⁷⁸ The authors concluded from these data “that there exists a group of CNCP patients whose long-term opioid consumption can be beneficial and remain moderate without them suffering from the consequences

⁹⁷⁴ *Id.* at pp. 260-261.

⁹⁷⁵ *Id.* at Appendix I, p. 47.

⁹⁷⁶ Boscarino, *et al.*, “Opioid-use disorder,” fn. 871, above, at p. 83.

⁹⁷⁷ Cowan DT, Wilson-Barnett DJ, Griffiths P, Vaughan DJA, Gondhia A, Allan LG. A randomized, double-blind, placebo-controlled, cross-over pilot study to assess the effects of long-term opioid drug consumption and subsequent abstinence in chronic noncancer pain patients receiving controlled-release morphine. *Pain Med.* 2005. doi:10.1111/j.1526-4637.2005.05020.x, at p. 113.

⁹⁷⁸ *Id.* at p. 116.

of problematic opioid drug use.”⁹⁷⁹ Appendix 1 states: “0% demonstrated psychological dependence.”⁹⁸⁰ This conclusion lacks validity for several reasons.

- i. The short duration without opioids is insufficient to assess “problematic opioid drug use.” This methodology might detect physical dependence and withdrawal, but not addiction. Addiction is a chronic relapsing and remitting illness evidenced by a pattern of behavior over weeks to months, not hours to days.
- ii. Craving and withdrawal are very subjective and not diagnostic of addiction. Further, asking study subjects about “craving” is likely to bias their response: “craving” is a loaded term associated with addiction. Patients would be savvy enough to want to avoid this pejorative label.
- iii. This British study was funded by Janssen-Cilag, introducing inherent bias.⁹⁸¹
- iv. Although this is a small study that would have little overall impact on the pooled analysis, it is worth attention if only to demonstrate the contradiction between Fishbain’s inclusion of an almost absurdly brief study of 60 hours of exposure, while omitting relevant studies with higher prevalence that he personally cited in his earlier review article.
- o. Higgins, *et al.*, performed a meta-analysis of incidence of addiction studies, that is, addiction diagnosed in a pre-specified period of time following the initial exposure to a prescription opioid. The authors argued for a 4.7% overall incidence of iatrogenic addiction to prescription opioids,⁹⁸² but their findings need to be considered in light of a number of limitations.
 - i. Higgins did not account for the role of dose and duration as the main cause of opioid use disorder. In particular, Higgins claimed to rely on the Edlund (2014) study for an incidence rate of 0.2%, while omitting Edlund’s finding that the rate in his healthcare database study was 50 times higher for those who were exposed to chronic (>90 days) high dose (>120 MME), compared to patients with only acute exposures (over 6% for the former, compared to 0.12% for the latter). Edlund noted that it was “almost meaningless to talk of a single ‘rate’”⁹⁸³ under these circumstances, yet that is precisely what Higgins did. Similarly, Higgins

⁹⁷⁹ *Id.* at p. 119.

⁹⁸⁰ *Id.* at Appendix 1.

⁹⁸¹ *Id.* at p. 113.

⁹⁸² Higgins C, Smith BH, Matthews K. Incidence of iatrogenic opioid dependence or abuse in patients with pain who were exposed to opioid analgesic therapy: a systematic review and meta-analysis. *Br J Anaesth.* 2018;120(6):1335-1344. doi:10.1016/j.bja.2018.03.009, p. 1339.

⁹⁸³ Edlund, “Role of Opioid Prescription”, fn. 76, above, at p. 562.

cited the Cepeda (2013) study for an overall rate of 0.5%, ignoring that this healthcare database study included all patients who “initiated” opioid therapy, without analysis of variations in rates between patients with different doses and durations of exposure.

- ii. Incidence will inevitably under-report the number of cases in a population, because it will only examine data for a fixed beginning and endpoint; whereas prevalence is the more accurate marker of the number of cases existing in a population at a given point in time, including all cases of addiction among the population taking prescription opioids. This is an important point, since a majority of OUD-diagnosed patients have recent medical prescriptions for opioids,⁹⁸⁴ such that their prescriptions are maintaining or contributing to their disorders, regardless of when onset of OUD occurred.⁹⁸⁵
- iii. New onset opioid use disorder (incidence) does not take into account the harm done to patients who maintain or relapse to opioid addiction as a result of medical exposure to opioids. That is, continued exposure imposes continued risk of misuse, dependence, overdose, and the panoply of ill effects of chronic opioid therapy described herein.
- iv. The authors speculate that the pooled rate was higher for the studies of “weak” opioids than for “strong” opioids because the subjects might have displayed “pseudoaddiction,”⁹⁸⁶ *i.e.*, because the opioids were weak, they displayed drug-seeking behaviors to alleviate their pain that were misconstrued by the physicians, rather than because of a use disorder. The report of a higher rate with lower doses is an unreliable, outlier finding that contradicts numerous large, well-done studies demonstrating the dose-response relationship between higher opioid dose and greater addiction and mortality. Also, Higgins’ comparison of “weak” versus “strong” opioids failed to meet standard methods of comparing the dose of prescription opioids according to their milligrams morphine equivalent, or MME.
- v. The authors’ restrictive criteria resulted in only 12 studies having been included⁹⁸⁷ compared to others (*e.g.*, Vowles), who included 38 studies.
- vi. The authors erroneously stated that Vowles reached a similar conclusion as to the rates of addiction (4.3 v. 4.7%),⁹⁸⁸ when in fact Vowles reported

⁹⁸⁴ Ali, “Opioid Use Disorder”, fn 84, above, at p. 156.

⁹⁸⁵ *Id.*, at p. 164.

⁹⁸⁶ Higgins C, Smith BH, Matthews K. Incidence of iatrogenic opioid dependence or abuse in patients with pain who were exposed to opioid analgesic therapy: a systematic review and meta-analysis. *Br J Anaesth*. 2018;120(6):1335-1344. doi:10.1016/j.bja.2018.03.009. at p. 1343.

⁹⁸⁷ *Id.* at p. 1335.

⁹⁸⁸ *Id.* at p. 1342.

rates of addiction as 8-12%,⁹⁸⁹ or approximately 21-29% when the spectrum of mild through severe OUD is included.

- vii. Two of three authors report pharma consulting, including Pfizer.⁹⁹⁰
- p. The 2010 Cochrane Review by Noble *et al.* (2010), stated that opioid addiction occurred in “0.27% of participants in the studies that reported that outcome,”⁹⁹¹ and “... serious adverse events, including iatrogenic opioid addiction, were rare.”⁹⁹² However, the underlying studies in the Cochrane Review that were selected for analysis were predominantly funded by the manufacturers and were neither intended nor designed to detect addiction risks. As detailed below, estimates based on those studies are unreliable and unrealistically low.
 - i. The Cochrane 2010 review analyzed 26 studies with 27 treatment groups that enrolled a total of 4,893 participants. Twenty five of the studies were case series or uncontrolled long-term trial continuations. The other was an RCT comparing two opioids.⁹⁹³ Only 8 of the 26 included studies provided data on addiction: Allan; Anderson; Hassenbusch; McIlwain; Milligan; Mystakidou; Portenoy; and Zenz.
 - ii. Only one of these studies (Portenoy, 2007)⁹⁹⁴ was *a priori* designed to assess risk of opioid use disorder/addiction. The rest were designed to assess pain efficacy, and addiction risk was an afterthought. Further, none applied rigorous detection methods, or in most cases any detection methods at all to assess opioid misuse or addiction. All of the studies excluded patients with a history of alcohol or substance use disorders. Seven of the eight studies were sponsored and/or written by industry authors, raising conflict of interest and bias issues.
- Below, I address in detail each of the eight studies providing data on addiction that were included in the 2010 Cochrane Review.
 - A. Allan *et al.* compared efficacy and safety of transdermal fentanyl and sustained release morphine in opioid naïve patients with chronic low back pain over 13 months.⁹⁹⁵ Classification as “opioid

⁹⁸⁹ Vowles, *et al.*, “Rates of Opioid Misuse,” fn. 847, above, at p. 569; McNicol, *et al.*, Cochrane Review 2013, fn. 777, above, at p. 28.

⁹⁹⁰ Higgins, *et al.*, “Incidence of Iatrogenic,” fn. 982, above, at p. 1343.

⁹⁹¹ Noble, *et al.*, “Long Term Opioid Management,” fn. 762, above, at p. 9.

⁹⁹² *Id.* at p. 2.

⁹⁹³ *Id.* at p. 1.

⁹⁹⁴ Portenoy, *et al.*, Long Term Use of Controlled-release Oxycodone for Noncancer Pain: Results of a 3-year Registry Study. *Clin. J. Pain* 2007; 23: 287-299, DOI: 10.1097/ 01.brs.0000186860.23078.a8.

⁹⁹⁵ Allan L, Richarz U, Simpson K, Slappendel R. Transdermal Fentanyl Versus Sustained Release Oral Morphine in Strong-Opioid Naïve Patients With Chronic Low Back Pain. *Spine* 2005; 30(22):2484-2490, at p. 2484.

naïve” was based on the patient receiving limited opioids in the 4 weeks prior to the study, with no screening for opioid use prior to 4 weeks.⁹⁹⁶ Opioid misuse and addiction did not warrant listing in the Adverse Event “Table 8.”⁹⁹⁷ In other words, it was not a variable the authors were measuring, as corroborated by the absence of any instrument to assess addiction, despite the use of other survey questionnaires used to track other adverse events.

I. Yet the authors claimed “Addiction was not reported as an adverse event for any participant.”⁹⁹⁸ The authors further stated “No cases of addiction were reported as an adverse event; this is in line with other studies, which have shown that opioids can be used in chronic noncancer pain without significant risk of abuse. [citing Jamison *et al.*, *Spine* 1998].”⁹⁹⁹

II. The authors’ conclusions are not reliable based on methodologic inadequacies to assess for addiction risk. Even when investigators are attempting to detect addiction and abuse, as in the studies described above, the difficulties are daunting, as indicated by reports of patient concealment of problem behaviors and substantial disparities between questionnaire responses and urine drug screening; when researchers do not look for addiction and abuse, they are quite unlikely to find such evidence. Further, the study was underwritten by Janssen pharmaceuticals, the makers of Duragesic, transdermal fentanyl, suggesting bias conferred by industry sponsorship.¹⁰⁰⁰

B. Anderson *et al.* followed 30 patients prospectively for 24 months to assess the long-term safety and efficacy of chronic intrathecal morphine (injected into the spinal canal, or into the subarachnoid space so that it reaches the cerebrospinal fluid) in the treatment of chronic pain.¹⁰⁰¹ Patients with “psychopathological or substance abuse problems” were screened out and deemed ineligible. Questionnaires were used to track many different variables, but none asked about signs and symptoms of opioid use disorder.

⁹⁹⁶ *Id.* at p. 2485.

⁹⁹⁷ *Id.* at p. 2488.

⁹⁹⁸ *Id.*

⁹⁹⁹ *Id.* at p. 2489.

¹⁰⁰⁰ *Id.* at p. 2484.

¹⁰⁰¹ Anderson VC, Ph D, Burchiel KJ. Prospective Study of Long-term Intrathecal Morphine in the Management of Chronic Nonmalignant Pain. *Neurosurgery* 1999;44(2), at p. 289.

- I. The authors report that one patient (1/30, 3%) “was withdrawn from therapy because of drug-seeking behavior”¹⁰⁰² This patient “complained of continually escalating pain after infusion system implant, despite successful pain relief during trial at an epidural dose of less than 10mg per day ... and sought to obtain oral narcotics from other health care providers,” although the authors do not disclose how they obtained this information. When further requests for dose increases were denied, the patient dropped out of the study.¹⁰⁰³
- II. The authors conclude “In general, the incidence of addiction among patients with nonmalignant pain receiving chronic opioid is low,” but their findings are unreliable given methodological failures to assess addiction risk. The study was sponsored by Medtronic, Inc., the makers of the intrathecal pump.¹⁰⁰⁴
- C. Hassenbusch, like Anderson, examined a case series of patients (22) with intrathecal opioid infusion pumps. In this case, they followed patients for 5 years.¹⁰⁰⁵ The same limitations described in the Anderson study apply here: patients with history of mental illness or addiction were excluded,¹⁰⁰⁶ and there were no screening instruments or any other detection method to assess for opioid misuse or addiction. Yet the authors conclude “There was no occurrence of opioid dependence, either physical or psychological”¹⁰⁰⁷
- D. McIlwain *et al.* did a 52-week open label extension study of oxymorphone extended release (ER) in patients with moderate to severe chronic osteoarthritis related pain.¹⁰⁰⁸ The study was sponsored by Endo Pharmaceuticals, the makers of the study drug.¹⁰⁰⁹ The study did not use screening instruments or other detection methods for opioid misuse or addiction. Their Table 2 of

¹⁰⁰² *Id.* at p. 292.

¹⁰⁰³ *Id.* at pp. 295-296.

¹⁰⁰⁴ *Id.* at p. 299.

¹⁰⁰⁵ Hassenbusch S, Stanton-Hicks M, *et al.* Long Term Intraspinal Infusions Of Opioids in the Treatment of Neuropathic Pain. *Journal of Pain and Symptom Management*. 1995;10:527-543, at p. 529.

¹⁰⁰⁶ *Id.* at p. 528.

¹⁰⁰⁷ *Id.* at p. 536.

¹⁰⁰⁸ McIlwain H, Ahdieh H. Safety, Tolerability, and Effectiveness of Oxymorphone Extended Release for Moderate to Severe Osteoarthritis Pain A One-Year Study. *Am J Ther*. 2005;112:106-112, p. 106.

¹⁰⁰⁹ *Id.* at p. 111.

adverse events did not include opioid misuse/addiction, despite including 11 other opioid-related adverse events.¹⁰¹⁰ Despite the absence of any method for detecting or measuring addiction risk, the authors concluded, “No instances of drug addiction or abuse were recorded.”¹⁰¹¹

- E. Milligan *et al.* studied 532 chronic noncancer pain patients (only 301 completed the trial) being treated with transdermal fentanyl for up to 12 months. They report “drug abuse/dependence” in less than 1% of their sample, but qualify this by saying, “none was considered definitely related to the treatment.”¹⁰¹² Like the other studies included in the addiction risk assessment of the 2010 Cochrane review, this study was not designed to reliably assess addiction risk: patients with a history of substance abuse or psychiatric disorders were excluded, no screening or detection instruments for opioid misuse or addiction were described.¹⁰¹³
 - I. The authors report three cases of “drug abuse (2 moderate and 1 severe)”; two cases of “moderate physical drug dependence (as opposed to abuse)”; and “no reports of addiction.”¹⁰¹⁴ Yet how these concepts were defined and the cases detected are not clarified.
 - II. The study was supported by a grant from Janssen.¹⁰¹⁵ Despite these serious flaws, the authors concluded, “There were no reports of addictive behavior in any of the patients during this long-term study. Because the fear of addiction is one of the reasons for the underuse of opioids in chronic noncancer pain, this study provides further evidence that these fears are unfounded.”¹⁰¹⁶ This conclusion does not follow from the evidence.
- F. The study by Mystakidou recruited 529 patients into an open-label study of transdermal therapeutic system-fentanyl (TTS-F) for 28 days, followed by an open-label follow-up for a median of 10

¹⁰¹⁰ *Id.* at p. 108.

¹⁰¹¹ *Id.* at p 109.

¹⁰¹² Milligan K, Lanteri-minet M, Borchert K, *et al.* Evaluation of Long-term Efficacy and Safety of Transdermal Fentanyl in the Treatment of Chronic Noncancer Pain. *J Pain*. 2001;2(4):197-204 at p. 197, doi:10.1054/jpai.2001.25352.

¹⁰¹³ *Id.* at p. 198.

¹⁰¹⁴ *Id.* at pp. 201-202.

¹⁰¹⁵ *Id.* at p. 197.

¹⁰¹⁶ *Id.* at p. 203.

months between 1996-2002.¹⁰¹⁷ The first page of the article includes the copyright symbol for the American Pain Society, which had been funded substantially by opioid manufacturers; the authors do not disclose a corporate sponsor, but they cite to prior studies of DelleMijn and Allan that acknowledged participation by Janssen-Cilag, the manufacturer of Duragesic TTS-F, and the Janssen Research Foundation.¹⁰¹⁸

- I. A complete description of exclusion criteria was not provided; the authors stated only, “Exclusion criteria included a history of opioid abuse, surgery in the preceding 7 days or scheduled surgery, contraindications to opioids, and opioids use outside of the designated treatment regimen.”¹⁰¹⁹ No information is provided as to what constituted “contraindications to opioids;” and the exclusion for “opioids use outside the designated treatment regimen” inherently eliminates the population with the most obvious defining characteristic of addiction.
- II. The authors state, “Following discontinuation from the study, no patient complained of withdrawal symptoms or was found to display dependency”¹⁰²⁰; however, like the others described above, the Mystakidou study included no protocol to detect addiction, withdrawal, dependency or abuse, either during the study or after discontinuation. Without such information, it is unknown whether patients experienced such effects during the study, nor whether they returned to their former opioid regimens after the study ended.
- G. Portenoy describes an open label continuation study using controlled release (CR) oxycodone (OxyContin) in a population of chronic pain patients who had previously participated in controlled trials of CR oxycodone for pain.
 - I. Unlike the other studies included in the 2010 Cochrane review, this study by Portenoy *et al.* included specific methods for assessing opioid misuse and addiction, including an independent review panel to determine types

¹⁰¹⁷ Mystakidou K, *et al.* Long-Term Management of Noncancer Pain With Transdermal Therapeutic System-Fentanyl. *J Pain*. 2003;4(6):298-306. doi:10.1016/S1526-5900(03)00632-1, at pp. 298-299.

¹⁰¹⁸ *Id.* at p. 305.

¹⁰¹⁹ *Id.* at p. 299.

¹⁰²⁰ *Id.* at pp. 300-301.

of problematic opioid use. However, the information evaluated by the independent review panel was based entirely on patient self-report, which we know to be inherently unreliable, particularly in the context of a clinical trial designed to assess pain efficacy.

- II. The authors reported “6 of 227 (2.6%) patients could be considered to have probable drug abuse or dependence based on the independent expert review, none of whom met diagnostic criteria for substance abuse.”¹⁰²¹ This appears to be the basis for the “3%” figure used in the Noble 2010 review. However, the article also reported that 133 patients dropped out of the study, so the use of 227 as the denominator is questionable. Further, “Patients with self-reported past or present substance or alcohol abuse” were excluded, as were patients with a “documented allergy to oxycodone or other opioids.”¹⁰²² Finally, the study was sponsored by Purdue Pharma, the makers of Oxycontin.¹⁰²³
- H. Zenz described 100 chronic nonmalignant pain patients who were given opioids in an open-label, non-controlled setting, between 1986-1990.¹⁰²⁴ Treatment was discontinued in 59 patients (21 did not respond to opioid therapy; 20 changed to an alternative treatment method; 10 were discontinued for “lack of compliance;” and 8 died during the study period).¹⁰²⁵
 - I. Zenz reported, “There were no cases of respiratory distress or addiction to opioids.”¹⁰²⁶ As in the studies described above, Zenz had no protocol to look for or record addiction or abuse.
 - II. No details were provided as to the type of “noncompliance” that caused 10 patients to be discontinued, but “noncompliance” in the setting of opioid therapy is a red flag for concern over signs of abuse as to which the lack of further information is another conspicuous weakness of the study.

¹⁰²¹ Portenoy, *et al.*, “Long Term Use,” fn. 994, above, at p. 296.

¹⁰²² *Id.* at p. 288.

¹⁰²³ *Id.* at p. 287.

¹⁰²⁴ Zenz M, *et al.* Long Term Oral Opioid Therapy in Patients with Chronic Nonmalignant Pain. *J Pain Symptom Manage.* 1992;7(2):69-77, at p. 70.

¹⁰²⁵ *Id.* at p. 73.

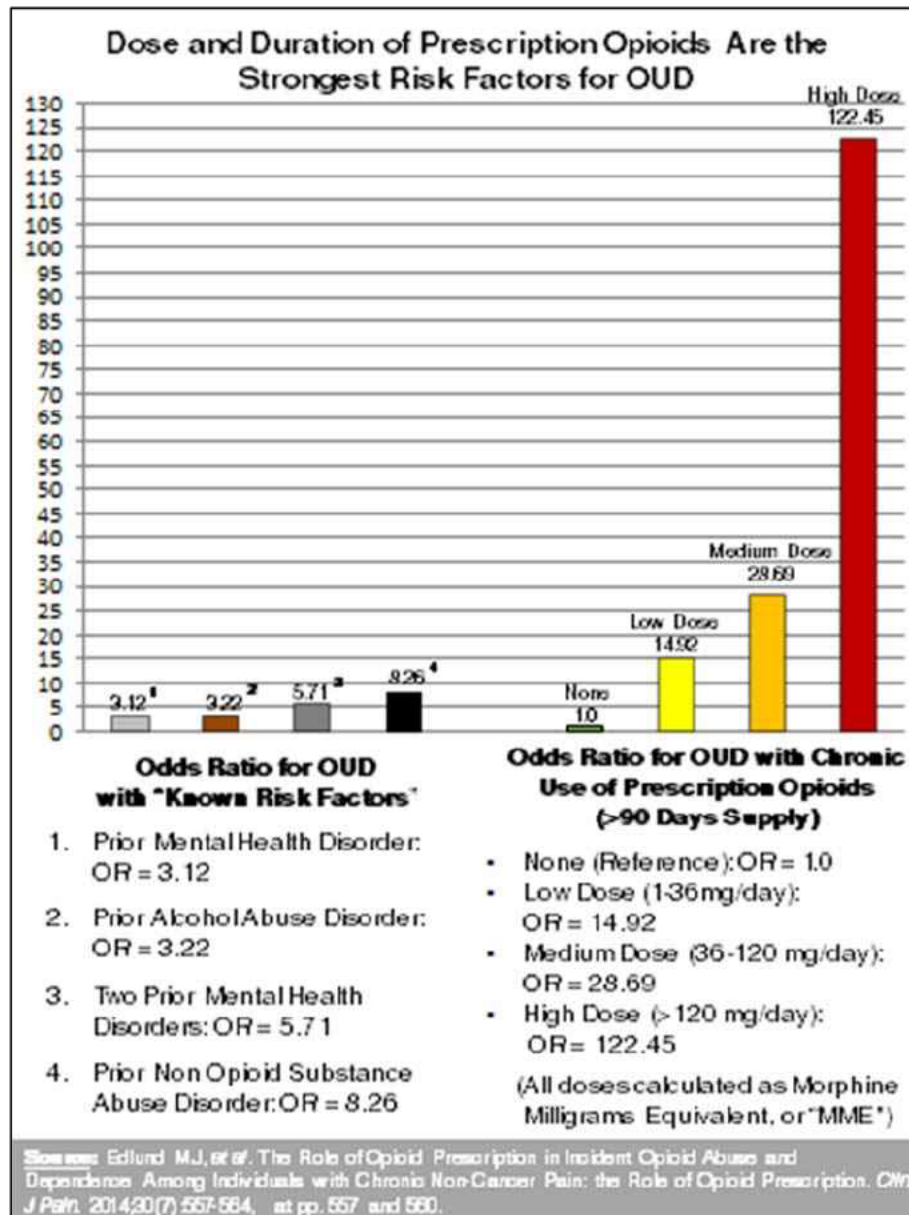
¹⁰²⁶ *Id.* at p. 69.

- iv. In summary, the studies contributing to the addiction rate reported in the 2010 Cochrane review are subject to common inadequacies, primary among them their focus on efficacy, lack of any method to detect addiction or misuse, and the screening out of higher risk patients. Their data do not square with the much higher prevalence of OUD reported among real world chronic pain populations, by investigators who were looking for it.
- v. As mentioned above, the 1980 New England Journal of Medicine letter to the editor entitled “Addiction Rare in Patients Treated with Narcotics,” reported only four cases of addiction among 11,882 patients treated with opioids.¹⁰²⁷ This letter did not represent relevant or reliable evidence of the risk of opioids for chronic non-cancer pain, because the article pertained to a hospitalized population, including patients who received no more than a single dose, rather than the outpatient chronic pain population for whom opioid use was promoted and became prevalent. Nonetheless, it influenced prescribers and was frequently quoted by the Pharmaceutical Opioid Industry in its advertisements for opioids in the treatment of chronic pain, as proving that “less-than-1%” of patients receiving opioids for pain becomes addicted. Defendants’ promotional messages continued to cite their “less-than-1%” claim, or that addiction with chronic opioid therapy was “rare,” despite numerous peer-reviewed studies to the contrary over a period of decades. (See Appendix I.)
- q. In summary, there is not, and has never been, scientific support for the claim that the risk of addiction from chronic opioid therapy is low, “rare,” or “less than 1%.” In fact, the best evidence available shows that the risk of addiction in patients taking opioids for chronic pain is between 10% and 30%. In teens and young adults, the evidence shows that even very limited exposure to prescription opioids can result in addiction.
- r. The Pharmaceutical Opioid Industry also made inaccurate claims as to the validity of patient screening as a predictor of who will become addicted. The largest risk factors for addiction are dose and duration of opioid exposure, regardless of whether a particular patient may have identifiable risk factors in his or her social or genetic history. It is difficult, if not impossible, to predict in advance who will and will not get addicted to a prescription opioid. When it occurs in patients taking opioid medications for pain, addiction is neither easy to identify nor easily managed.
- Over the years of increased use of opioids for chronic pain, as the epidemic of addiction has grown, a number of physicians have attempted to develop “screening” instruments that might identify patients at high risk of addiction, who could then be screened out of opioid therapy, or closely

¹⁰²⁷ Porter, Jick, “Addiction Rare,” fn. 168, above, at p. 123.

monitored if such therapy were instituted. However, even if screening for established risk factors were implemented, data support the conclusion that OUDs would not be eliminated. In the Edlund study, the odds ratio for the incidence of OUDs associated with chronic use, even at low doses, was far higher than the odds ratio for established risk factors that screening instruments attempt to identify. In particular, the odds ratios with chronic low dose use (14.92), medium (28.69), and high dose (122.45) were all substantially greater than the odds ratios for mental health diagnosis (3.12); multiple mental health diagnoses (5.71); prior alcohol use disorder (3.22); and prior non-opioid abuse disorder (8.26).¹⁰²⁸ For chronic/high dose opioid use, the odds ratio of approximately 122 is 40 times greater than for a mental health or alcohol use diagnosis, and 15 times higher than for a prior non-opioid use disorder. According to these data, the chronic use of opioids is responsible for far more OUDs than the existence of identifiable risk factors for OUDs. These data are shown in the graph below:

¹⁰²⁸ Edlund, *et al.*, “Role of Opioid Prescription,” fn.76, above, at p. 563.



- ii. It is true that *a priori* risk of addiction is related to genetics (a biological parent or grandparent with addiction), as well as complex psychosocial factors such as co-occurring mental illness, poverty, unemployment, multigenerational trauma, and peer influence. Persons with a history of addiction are more likely to develop problematic opioid use to the opioid their doctor is prescribing.¹⁰²⁹ These risk factors notwithstanding, it is also true that addiction can occur in persons with none of these risk factors, and it is difficult, if not impossible, to predict in advance who will and will not

¹⁰²⁹ Weisner CM, Campbell CI, Ray GT, et al. Trends in prescribed opioid therapy for non-cancer pain for individuals with prior substance use disorders. *Pain*. 2009;145(3):287-293, p. 292.

get addicted to a prescription opioid. Hence, caution and monitoring are necessary for all patients being prescribed these medications, and even then there will never be a failsafe method.

- iii. A validated screening instrument to predict which patients are more vulnerable to the adverse consequences of opioid therapy, including addiction, is theoretically of benefit, but to date, none has been shown to predict future adverse consequences. Kaye *et al.* summarizes the progress in a narrative review as follows: “Although several screening instruments and strategies have been introduced in recent years, there is no single test or instrument which can reliably and accurately predict those patients not suitable for opioid therapy or identify those who need increased vigilance or monitoring during therapy.”¹⁰³⁰
- iv. Chou *et al.*, in reviewing four studies that evaluated the accuracy of risk assessment instruments, found that three studies reported “inconsistent results” for the 10-item Opioid Risk Tool and that “No study evaluated the effectiveness of risk mitigation strategies for improving outcomes related to overdose, addiction, abuse, or misuse.”¹⁰³¹
- Indeed the Opioid Risk Tool, which was touted by Defendants for screening patients who could “safely” be prescribed opioids, has recently been invalidated. “In this population, we were not able to replicate the findings of the initial ORT study. Self-report was *no better than chance* in predicting those who would have an opioid aberrant behavior. The ORT risk variables did not predict aberrant behaviors in either gender group. There was significant disparity in the scores between self-reported ORT and the ORT supplemented with medical record data (enhanced ORT).”¹⁰³²
- vi. There is a potential risk of any opioid risk tool: that prescribers gain a false sense of knowing who can and cannot get addicted, when in fact the biggest predictors of opioid dependency and addiction are access to opioids in the first place, and dose and duration, not personal characteristics. Indeed this focus on risky patients, rather than the inherent

¹⁰³⁰ Kaye A, Jones M, Kaye A, *et al.* No Prescription Opioid Abuse in Chronic Pain: An Updated Review of Opioid Abuse Predictors and Strategies to Curb Opioid Abuse: Part 1. Title. *Pain Physician J.* 2017, at p. 573. This conclusion was reaffirmed in a very recent review that concluded: “Despite their widespread use, most screening tools involving combinations of questions were based on low-quality studies or, when diagnostic performance was assessed among high-quality studies, *demonstrated poor performance in helping to identify patients at high vs low risk.*” Klimas, *et al.*, Strategies to Identify Patient Risks of Prescription Opioid Addiction When Initiating Opioids for Pain: A Systematic Review. *JAMA Netw Open.* 2019;2(5):e193365. doi:10.1001/jamanetworkopen.2019.3365.

¹⁰³¹ Chou, *et al.*, “Effectiveness and Risks – Systemic,” fn. 761, above, at p. 280.

¹⁰³² Clark MR, Hurley RW, Adams MCB. Re-assessing the Validity of the Opioid Risk Tool in a Tertiary Academic Pain Management Center Population. *Pain Med.* 2018;19(7):1382-1395. <http://dx.doi.org/10.1093/pm/pnx332>, at p. 1382.(emphasis added).

risk associated with opioids themselves, has been prevalent among prescribers in the 1980s, 1990s, and 2000s who were encouraged by the Defendants to rely on such tools, and it is in part responsible for the opioid epidemic we face today. Prescribers were incorrectly taught that by screening out high risk patients, they would avoid opioid misuse and addiction. For example, Janssen also promoted the concept that “the potential for addiction is in the patient, not the opioid” and defined high risk as “long-term exposure to opioids in addicts.”¹⁰³³ Both of these statements are false and misleading: opioids are inherently addictive and long-term exposure is a significant risk factor even in patients without other risk factors for addiction. Also, as discussed in this Report, abundant scientific literature demonstrates that even short-term exposure will result in chronic use and its attendant problems of addiction and dependence in a significant subset of patients.

- The impact of the dose-duration risks of prescribed opioids will be felt for years, as evidenced by a recent study of OUD among hospitalized chronic pain patients which found that “prevalence of OUD increased substantially from 2011 to 2015...increas[ing] from 109,222 in 2011 to 172,680 in 2015 (P< 0.001).”¹⁰³⁴ As patients are exposed to opioids for longer durations, the risk for developing OUD rises.
- viii. Further, prescribers who relied on Pharmaceutical Opioid Industry statements regarding the great benefits and minimal risks of prescribing opioids for pain would also gain a false sense that there was little or no need for screening.
- ix. It is unlikely that asking patients about risk factors will ever be a suitable method of screening, as motivation to minimize or omit risk factors in pursuit of obtaining a specific type of drug will weigh heavily on the truthfulness and transparency of reporting (*See* discussion of Fleming study, above). As noted in a very recent JAMA review, “Despite their widespread use, most screening tools involving combinations of questions were based on low-quality studies or, when diagnostic performance was assessed among high-quality studies, demonstrated *poor performance in helping to identify patients at high vs low risk.*”¹⁰³⁵
- x. Finally, Defendants were well aware that primary care physicians (PCPs), had neither the skills nor the resources to effectively monitor their patients for the development of opioid misuse and addiction, but nonetheless targeted these providers to promote sales.

¹⁰³³ JAN-MS-00310473, produced in native at *11-12.

¹⁰³⁴ Orhurhu V et al. Trends of opioid use disorder among hospitalized patients with chronic pain. *Pain Practice*. 2019;19(6): 656-663, at p. 656.

¹⁰³⁵ Klimas,, “Strategies to Identify”, fn. 661, above, at p.1. (emphasis added).

- A. At a 2001 Scientific Advisory Board meeting for Janssen Duragesic, it was evident that Janssen was targeting front line providers, i.e. PCPs to promote Duragesic.¹⁰³⁶
- B. At the same time and at the same meeting, Janssen and its advisors were well aware the PCPs were not adequately trained to track opioid misuse and addiction: “Physicians are writing more opioid prescriptions, but they do not know how to monitor patients.”¹⁰³⁷
- C. Janssen’s own advisors conceded that even with training, it is extremely difficult to tell which patients will develop an opioid misuse problem: “Preliminary findings show that information or impressions gained in the doctor-patient relationship cannot predict which patients will have a positive urine toxicology screen. Even urine tox screens may not be reliable as they vary, and some have low sensitivities to oxycodone and fentanyl.”¹⁰³⁸
- D. Yet despite these tangible and openly recognized limitations, Defendants launched an aggressive marketing campaign targeting prescribers, which misrepresented the facts on risk of addiction and validity of screening, and instead aggressively promoted uptitrating of their products.¹⁰³⁹

9. Increased supply of prescription opioids contributed substantially to more individuals becoming addicted to opioids and transitioning from prescription opioids to illicit sources of opioids such as heroin and fentanyl (The Gateway Effect).

- a. There is a clear causal link between prescription opioid exposure, prescription opioid misuse, and opioid addiction. Opioid misuse, or non-medical use of prescription opioids (“NMUPO”)¹⁰⁴⁰, is defined as taking an opioid medication outside of a prescribed indication.¹⁰⁴¹ With increased opioid prescribing in the United States, more Americans have been exposed to prescription opioids at higher doses and for longer durations (including those not directly prescribed the opioid), contributing to rising incidence and prevalence of opioid misuse, dependence, addiction, and overdose death.¹⁰⁴² These are the expected and natural consequences of exposing large populations to addictive and dangerous drugs, particularly where tolerance requires users to increase the dose to achieve the same effect, resulting in ever-greater risk of harm.

¹⁰³⁶ JAN-MS-00481055

¹⁰³⁷ *Id.* at 1062.

¹⁰³⁸ *Id.* at 1064.

¹⁰³⁹ See JAN-MS-00779345, FDA Warning Letter to Janssen, RE: NDA #19-813, September 2, 2004.

¹⁰⁴⁰ NMUPO is sometimes referenced as “NUPO”, nonmedical use of prescription opioids.

¹⁰⁴¹ NASEM Report (2017), fn. 51, above, at p. 152.

¹⁰⁴² *Id.*, at p. 193

- b. According to the Ohio Governor’s Cabinet Opiate Action team, in 2013 “Up to 50% of patients using opioid therapy for chronic, non-cancer pain misuse their medication. After hearing from 81 witnesses, the study committee learned that some addicts get hooked after snorting opioid pills or abusing the drugs in another way with friends; they typically get these pills from family and friends who have them sitting around in their medicine cabinets. The other group of addicts started with a valid medical prescription and ended up with an addiction. People can become addicted in a matter of weeks using opioids, while addiction takes years with alcohol and other drugs. The human body and brain quickly develops a tolerance to opioids, so it takes a progressively higher dosage to get the same high.”¹⁰⁴³
- c. Teens are especially vulnerable to the increased access to prescription drugs. Adolescence is a time when the rapidly growing brain is more plastic, and therefore more vulnerable on a neurological level, to potentially irreversible brain changes caused by chronic drug exposure. Teens are also more likely to take risks, without appreciating the adverse consequences associated with those risks.¹⁰⁴⁴
- d. In 2012, some 1.9 million individuals aged 12 or older misused a prescription drug for the first time within the past twelve months, an average of 1,350 initiatives per day. Prescription drugs now rank fourth among the most-misused substances in America, behind alcohol, tobacco, and cannabis. They rank second among teens. Of those who became addicted to any drug in the previous year, a quarter started out using a prescription medication: 17 percent began with opioid pain relievers, 5 percent with sedative-hypnotics, and 4 percent with stimulants.¹⁰⁴⁵
- e. In 2017, McCabe *et al.* found, “Adolescents who reported both medical and nonmedical use of prescription opioids were more likely to indicate medical use of prescription opioids before initiating nonmedical use...” (“NUPO”)¹⁰⁴⁶ “The findings provide compelling evidence that medical use of prescription opioids and NUPO are highly correlated, especially among adolescents. . . . We found that the majority of NUPO involved a history of medical use, and this finding should provide some concern to health professionals who prescribe opioid medications to adolescents, given the serious health consequences associated with NUPO.”¹⁰⁴⁷ McCabe’s reference for this point included the Compton (2016) article (cited in §8.g.vi, below), that described the trajectory from non-medical use to illicit opioids, thus emphasizing that McCabe is referring to the “Gateway Effect”

¹⁰⁴³ Ohio House, “Chairman’s Report”, fn. 71, above, at p. 6.

¹⁰⁴⁴ Lembke, Drug Dealer MD, fn. 2, above, at pp. 26 and 48.

¹⁰⁴⁵ *Id.*, at pp. 25-26.

¹⁰⁴⁶ McCabe, Sean Esteban, *et al.* Trends in medical and nonmedical use of prescription opioids among US adolescents: 1976–2015. *Pediatrics* 139.4 (2017): e20162387, at p. 1.

¹⁰⁴⁷ *Id.* at p. 8.

transition, i.e., from initial medical use, to subsequent non-medical use, and ultimately to illicit opioids.

- f. In 2019, McCabe *et al.* found that almost one in every two high school seniors who reported the medical use of prescription opioids after initiating NMUPO had two or more substance use disorder (addiction) symptoms at age 35.¹⁰⁴⁸
 - i. These data show that teens who are exposed to prescription opioids without a prescription will often be further exposed through a subsequent medical prescription, and as a result are at increased risk of developing an opioid addiction later in life (above what their risk would have been with non-medical use alone). The cumulative effect of prescription opioid exposure, through both medical and non-medical use, causally leads to opioid addiction.¹⁰⁴⁹
 - ii. The authors write, “These results indicate substantial risk for developing SUD among adolescents who have already initiated NMUPO and reinforce the critical role of screening when prescribing opioid analgesics to adolescents.”¹⁰⁵⁰ While the authors suggest that screening can play a role in mitigating future opioid addiction, screening tools have been shown to have limited efficacy in identifying at risk patients.¹⁰⁵¹ The more significant goal is to reduce access to prescription opioids, which increases risk by increasing exposure to both medical and subsequent non-medical use.
- g. In 2020, McCabe *et al.* reported upon the longitudinal relationship between U.S. teens’ prescription opioid use (medical and non-medical) and subsequent heroin use in adulthood.¹⁰⁵² From more than 11,000 survey respondents, they found that adolescents who reported either medical use or non-medical use of prescription opioids were at greater risk of progressing to heroin use in adulthood than population controls.¹⁰⁵³
 - i. The McCabe 2020 study definitively supports the conclusion that medical users of prescription opioids transition to heroin use, regardless of

¹⁰⁴⁸ McCabe SE, Veliz PT, Boyd CJ, Schepis TS, McCabe V V., Schulenberg JE. A prospective study of nonmedical use of prescription opioids during adolescence and subsequent substance use disorder symptoms in early midlife. *Drug Alcohol Depend.* 2019. doi:10.1016/j.drugalcdep.2018.10.027, at p. 379.

¹⁰⁴⁹ *Id.* at p. 381.

¹⁰⁵⁰ *Id.* at p. 383.

¹⁰⁵¹ Clark MR, Hurley RW, Adams MCB. Re-assessing the Validity of the Opioid Risk Tool in a Tertiary Academic Pain Management Center Population. *Pain Med.* 2018;19(7):1382-1395. <http://dx.doi.org/10.1093/pm/pnx332>, at p. 1382.

¹⁰⁵² McCabe SE, Boyd CJ, Evans-Polce J, McCabe VV, Schulenberg JE, Veliz PT. From Pills to Powder: A 17-year transition from prescription opioids to heroin among US adolescents followed into adulthood. *J Addict. Med.* 2020;1-4, at p. 1.

¹⁰⁵³ *Id.*

intervening non-medical use. In more recent cohorts in the population sample in the McCabe 2020 study, 7% of teens who reported prescription opioid medical use only went on to use heroin in adulthood, for an adjusted odds ratio of 2.68 (95% CI 1.01, 7.17).¹⁰⁵⁴

- ii. Further, McCabe *et al* report that among their sample population already using heroin by age 18 (n=179), 22% used heroin following non-medical use of prescription opioids, and 39% used heroin and prescription opioids non-medically within the same year and 13% misused prescription opioids after initiating with heroin.¹⁰⁵⁵ The increased access and supply of prescription opioids has increased the risk of teenagers and young adults being exposed to any opioid. Prescription opioid use and heroin use are inextricably intertwined.
- h. Writing in the journal *Pediatrics* (2018) Harbaugh *et al.* report that “The majority of US high school seniors with both medical use and nonmedical use of prescription opioids reported medical use before initiating nonmedical use of prescription opioids, suggesting a role of leftover prescriptions in the transition to a nonmedical use of prescription opioids. This may be due, in part, to the perception that prescription opioids are safe if they are prescribed by physicians despite the fact that the addiction potential is similar to heroin.”¹⁰⁵⁶
- i. There is a clear causal link between prescription opioid exposure and the subsequent use of heroin and other illicit opioids.
 - i. The natural history of the disease of addiction is that individuals with addiction require increasing amounts and/or more potent forms over time to overcome tolerance, to maintain physiologic homeostasis, and to avoid painful withdrawal.
 - ii. Scientific literature supports the conclusion that greater exposure to prescription opioids is associated with greater transition to heroin. An authoritative CDC study concluded, “Frequent nonmedical users - people reporting 100-365 days of PYNMU [Per Year Nonmedical Use] - had the highest rate of past year heroin use and were at increased risk for ever injecting heroin (aOR 4.3, 95% CI 2.5-7.3) and past year heroin abuse or dependence (aOR 7.8, 95% CI 4.7-12.8) compared to infrequent nonmedical users (1-29 days of PYNMU).”¹⁰⁵⁷ Note that this study relied on NSDUH data, which investigated only nonmedical users of prescription

¹⁰⁵⁴ *Id.*, at Table 2.

¹⁰⁵⁵ *Id.*, at p. 3.

¹⁰⁵⁶ Harbaugh CM, Lee JS, Hu HM, *et al.* Persistent Opioid Use Among Pediatric Patients After Surgery. *Pediatrics*. 2018;141(1):e20172439, at p. 5.

¹⁰⁵⁷ Jones CM, Heroin use and heroin use risk behaviors among nonmedical users of prescription opioid pain relievers – United States, 2002-2004 and 2008-2010. *Drug Alcohol Depend.* 2013;132(1-2):95-100, at p.

opioids; therefore the study does not mean that medical users are somehow immune to the risk of transition to heroin. To the contrary, as demonstrated by McCabe, subjects who had only reported medical use of prescription opioids experienced a statistically significant, 2.68-fold increased risk of transition to heroin use.¹⁰⁵⁸

- iii. The finding of greater transition to heroin with more prescription opioid use provides an example of a dose-response relationship between exposure to a risk factor and the occurrence of an adverse outcome, and such a dose-response relationship is a hallmark of cause and effect. Further, the adjusted Odds Ratio (aOR) of 4.3, as reported in the CDC study, above, falls within the range of “strong” associations, another indicator of cause and effect between exposure to prescription opioids and the outcome of heroin abuse. See Section Section §C.13 of this Report for a detailed discussion of the factors considered in determining whether an association is likely to be causal.
- iv. As increasing numbers of Americans became addicted to prescription opioids over the past two decades, they were forced to seek out cheaper and more potent opioids. The illicit drug market met that increased demand with cheap and available heroin and fentanyl. Fentanyl, which is 50-100 times more potent than heroin and comes in white powder form similar to heroin, made its way into the illicit market without users realizing what they were ingesting, resulting in a surge of fentanyl related overdose deaths.¹⁰⁵⁹
- “A preponderance of evidence suggests that the major increase in prescription opioid use beginning in the late 1990s has served as a gateway to increased heroin use¹⁰⁶⁰...The interrelated nature of the prescription and illicit opioid epidemics means that one cannot be addressed separately from the other.”¹⁰⁶¹
- vi. In the 1960s, 80% of opioid users reported that their first exposure to opioids was in the form of heroin. By the 2000s, however, 75% of opioid

¹⁰⁵⁸ McCabe SE, Boyd CJ, Evans-Polce J, McCabe VV, Schulenberg JE, Veliz PT. From Pills to Powder: A 17-year transition from prescription opioids to heroin among US adolescents followed into adulthood. *J Addict. Med.* 2020;1-4, at Table 2.

¹⁰⁵⁹ “IMF [illicitly manufactured fentanyl] is most commonly mixed with or sold as white powder heroin.” Gladden RM, Martinez P, Seth P. Fentanyl Law Enforcement Submissions and Increases in Synthetic Opioid-Involved Overdose Deaths — 27 States, 2013–2014. *MMWR Morb Mortal Wkly Rep* 2016;65:837–843, at pp. 836, 840-841. DOI: <http://dx.doi.org/10.15585/mmwr.mm6533a2external> icon.

¹⁰⁶⁰ NASEM Report (2017) at fn. 51, above at p. 215. See also discussion of Paulozzi (2006), supra, at §3.C.ii-iii.

¹⁰⁶¹ *Id.* at p. 248.

users reported that their first exposure to opioids was in the form of prescription painkillers.¹⁰⁶²

- vii. In a study based on NSDUH data from 2002-2011, the incidence of heroin use among people who reported prior nonmedical use of prescription opioids was 19 times as high as the incidence among persons who reported no previous nonmedical use.¹⁰⁶³
- viii. Prescription opioid use disorder/addiction is associated with a likelihood of heroin addiction that is 40 times as great as the likelihood with no prescription-opioid misuse or addiction, even after accounting for sociodemographic, geographic, and other substance abuse or dependence characteristics.¹⁰⁶⁴
- ix. Eighty-six percent of urban people who used injected heroin in New York and Los Angeles in 2008 and 2009 had used prescription opioids nonmedically before using heroin.¹⁰⁶⁵ Similar studies conducted in San Diego, Seattle, and New York showed that 40%, 39%, and 70% of heroin users, respectively, reported that they had used prescription opioids nonmedically before initiating heroin use.¹⁰⁶⁶
- Muhuri found that 79.5% of persons who recently began using heroin had used prescription opioids nonmedically before initiating heroin use.¹⁰⁶⁷
- A study of heroin users in Wilmington, Delaware, found that “most reported that prescription opioids were indeed their gateway to heroin use.”¹⁰⁶⁸
- xii. A 2014 research paper evaluating transitions from opioid pills to heroin injecting in Philadelphia and San Francisco, concluded that, “Unlike those

¹⁰⁶² Cicero TJ, Ellis MS, Surratt HL, Kurtz SP. The changing face of heroin use in the United States: A retrospective analysis of the past 50 years. *JAMA Psychiatry*. 2014. doi:10.1001/jamapsychiatry.2014.366, at p. E-1.

¹⁰⁶³ Muhuri PK, Gfroerer JC, Davies MC. Associations of nonmedical pain reliever use and initiation of heroin use in the United States. *CBHSQ Data Rev*. 2013;(August):1-16, at p. 1.

¹⁰⁶⁴ Compton WM, Jones CM, Baldwin GT. Relationship between Nonmedical Prescription-Opioid Use and Heroin Use. *N Engl J Med*. 2016. doi:10.1056/NEJMr1508490, at p. 157.

¹⁰⁶⁵ Lankenau SE, Teti M, Silva K, Bloom JJ, Harocopos A, Treese M. Initiation into prescription opioid misuse amongst young injection drug users. *Int J Drug Policy*. 2012;23(1):37-44, at p. 41.

¹⁰⁶⁶ Compton, *et al.*, “Relationship Between NPOU and Heroin Use,” fn. 1064, above, at p. 156.

¹⁰⁶⁷ Muhuri, *et al.*, “Associations of NMPRU and Heroin,” fn. 1063, above, at p. 1.

¹⁰⁶⁸ Inciardi JA, *et al.*, Prescription Opioid Abuse and Diversion in an Urban Community: The Results of an Ultra-Rapid Assessment. *Pain Medicine*. 2009;10:537-548, at p. 544.

substances previously labeled ‘gateway drugs’, opioid pills seem to have a direct relationship with progression to heroin initiation.”¹⁰⁶⁹

- xiii. A recent article by Pielech, *et al.*, stated, “Emerging data indicate that *any* exposure to opioids as an adolescent (medical or non-medical) appears to present short and long term risks for initiating heroin and prescription opioid use.”¹⁰⁷⁰

■ The number of Americans aged 12 and older with past month heroin use, rose from 281,000 to 335,000 between 2011 and 2013, a significant increase from the 166,000 using heroin in 2002.¹⁰⁷¹

- xv. In 2017, more than 28,000 deaths in the United States involved a synthetic opioid, primarily fentanyl, more deaths than from any other type of opioid.¹⁰⁷²

- j. The epidemic of prescription opioid misuse, addiction, and overdose death beginning in the 1990s has been a significant factor contributing to the subsequent increase in heroin and fentanyl misuse, addiction, and overdose death. Further, the Pharmaceutical Opioid Industry knew that prescription opioids are a gateway to illicit opioids. In March 2011, Purdue’s “Hair Testing Advisory Panel,” convened to help make the argument in favor of OxyContin’s “tamper-resistant formulation,” concluded that one of the “anticipated impacts of reformulation” was “reducing *OxyContin’s* role as a gateway drug” for recreational users.¹⁰⁷³
- k. Increased access/exposure to prescription opioids contributed not only to increased heroin and illicit fentanyl death; it also contributed to increased non-opioid overdose deaths, including sedatives and stimulants. A 2020 study by Segel *et al.*, in examining the relationship between state-level opioid overdose death rates at the beginning of the opioid epidemic (1999-2004) and overdose death rates for opioids and other substances in later years (2005-2018), found the following: “our results suggest two characteristics of the opioid crisis: persistence and pervasiveness. In adjusted analysis, we found that for each additional opioid overdose death per 100,000 population at baseline, states had 23.5 more opioid deaths, 4.4 more heroin deaths, 8.0 more synthetic opioid deaths, 9.2 more sedative deaths, 3.3 more stimulant deaths, and 4.6 more cocaine deaths per

¹⁰⁶⁹ Mars SG, *et al.*, “Every ‘Never’ I Said Came True”: Transitions from Opioid Pills to Heroin Injecting. *Int’l J. of Drug Policy*. 2014;25:257-266, at p. 264

¹⁰⁷⁰ Pielech, *et al.*, Receipt of Multiple Outpatient Prescriptions Is Associated With Increased Risk of Adverse Outcomes in Youth: Opioid Prescribing Trends, Individual Characteristics, and Outcomes from 2005-2016. *PAIN* 2020, published ahead of print. DOI:10.1097/j.pain.0000000000001812, at p. 2 (emphasis in original).

¹⁰⁷¹ McCarthy M. Illicit drug use in the US holds steady, but heroin use is on rise. *BMJ*. 2013;347(September):f5544. doi:10.1136/bmj.f5544, at p. 1.

¹⁰⁷² Centers for Disease Control and Prevention. *Synthetic Opioid Overdose Data*, (Apr. 2, 2019) <https://www.cdc.gov/drugoverdose/data/fentanyl.html>.

¹⁰⁷³ PPLP003370086 at 0106 (emphasis added).

population from 2005 to 2018.”¹⁰⁷⁴ In sum, “After adjusting for sociodemographic and state-level differences, baseline opioid overdose death rates in 1999-2004 were significantly associated with future opioid- and non-opioid-related overdose death rates.”¹⁰⁷⁵ The association reported by Segel *et al.* is likely to be causal because of the known phenomena of reinstatement (relapse) and cross-addiction, wherein patients addicted to prescription opioids are more susceptible to addiction to other drugs, especially when their drug of choice is not available.

- i. Neuroscientists have shown that brain changes that occur after continuous heavy use of addictive substances can cause damage that does not resolve even after years of abstinence. One of the ways these irreversible changes can manifest is that the brain is primed to relapse to addictive physiology even after a single exposure to the addictive substance.¹⁰⁷⁶ This is called “reinstatement” by neurobiologists, and “relapse” by those who are addicted.
- ii. Reinstatement is not triggered solely by the substance that the individual was previously addicted to. Reinstatement can occur with any addictive substance because all drugs of abuse work on the same brain reward pathway.¹⁰⁷⁷ For example, animals repeatedly exposed to the addictive component of marijuana (tetrahydrocannabinol, or THC) and then not given THC for a period of time become addicted to morphine more quickly than animals not previously exposed to THC.¹⁰⁷⁸ This phenomenon is called cross-sensitization, or cross-addiction. Individuals who are addicted to opioids are consequently more susceptible to addiction to other drugs, including sedatives and stimulants.

10. Increased supply of prescription opioids contributed substantially to more individuals, including newborns, becoming dependent on opioids, increasing their risk for opioid-related morbidity and mortality (The Dependence Effect).

- a. Prescription opioids induce physiological dependence almost universally, and dependence leads to addiction in a significant subset of users, particularly as dose and duration of exposure are increased.
- b. Over the last 30 years, the liberal prescribing of opioids for chronic pain has created a “legacy” population of patients who have been on opioids for several

¹⁰⁷⁴ Segel JE, *et al.* Persistence and Pervasiveness: Early wave opioid overdose death rates associated with subsequent overdose death rates. *Public Health Reports.* 2020;00(0):1-7, at p. 1.

¹⁰⁷⁵ *Id.*, at p. 3.

¹⁰⁷⁶ Steketee JD, Kalivas PW. Drug Wanting: Behavioral sensitization and relapse to drug-seeking behavior. *Pharmacol Rev.* 2011;63:348-365.

¹⁰⁷⁷ Nestler EJ, Is there a common molecular pathway for addiction? *Nature Neuroscience.* 2005;8(11):1445-1449.

¹⁰⁷⁸ Cadoni C, *et al.* Behavioral sensitization after repeated exposure to Δ9-tetrahydrocannabinol and cross-sensitization with morphine. *Psychopharmacology.* 2001;158:259-266, at p. 266.

years if not decades, and are now physically dependent on opioids, making it difficult to come off (The Dependence Effect).

- c. Physiologic dependence, as currently defined by the DSM-5, is not the same as addiction. Dependence is the process whereby the body comes to rely on the drug to maintain biochemical equilibrium. When the drug is not available at expected doses or time intervals, the body becomes biochemically dysregulated, which manifests as the signs and symptoms of withdrawal. Although opioid dependence as currently defined is not the same as addiction, dependence on opioids can be associated with significant morbidity and mortality, and thus is not the same thing as dependence on other medications used as evidence-based treatment for illness.¹⁰⁷⁹ Also, while dependence is defined differently from addiction, the line between them is not well-defined; in particular, the evidence of addiction often comes when an opioid-dependent patient attempts to taper and discovers that the loss of the drug causes the craving and compulsion that define addiction. In my clinical experience, dependence in some individuals can develop quickly. This clinical experience is consistent with studies showing that even short-term prescriptions of opioids for acute injuries result in long-term use of opioids after the acute condition has passed.¹⁰⁸⁰ In the DSM-4, the edition prior to the DSM-5, “opioid use disorder” was called “opioid dependence.” The new DSM-5 criteria made it more difficult to diagnose Opioid Use Disorder (opioid addiction), by removing the criteria of withdrawal, and tolerance from the definition in the case of a patient taking prescribed opioids under a doctor’s care. The DSM-5 thereby reduced the proportion of patients who could be diagnosed with opioid use disorder.
- d. By 2005, long-term opioid therapy was being prescribed to approximately 10 million Americans. “In 2014 alone, U.S. retail pharmacies dispensed 245 million prescriptions for opioid pain relievers. Of these prescriptions, 65% were for short-term therapy (<3 weeks), but 3 to 4% of the adult population (9.6 million to 11.5 million persons) were prescribed longer-term opioid therapy.”¹⁰⁸¹
- e. Once established, opioid dependence represents a complex, debilitating, and sometime irreversible clinical problem. In some cases, the suffering from withdrawal is so extreme that patients say they would rather die than go through it. Indeed, people can die from opioid withdrawal, due to vital sign instability, suicide, and other complications.

¹⁰⁷⁹ Lembke, *et al.*, “Weighing the Risks,” fn. 4, above.

¹⁰⁸⁰ Delgado M, *et al.* National Variation in Opioid Prescribing and Risk of Prolonged Use for Opioid-Naive Patients Treated in the Emergency Department for Ankle Sprains. *Ann Emerg Med.* 2018, at p. 1; *see also* Howard R, Fry B, Gunaseelan V, *et al.* Association of Opioid Prescribing with Opioid Consumption after Surgery in Michigan. *JAMA Surgery.* 2018, at p. E-6.

¹⁰⁸¹ Volkow, *et al.*, “Misconceptions and Mitigation,” fn. 44, above, at p. 1253.

- f. Opioids cause neuroadaptation¹⁰⁸² and lead to tolerance, physiologic dependence, and painful withdrawal, even without the more complex biopsychosocial disease of addiction. As such, tolerance, dependence, and withdrawal in and of themselves represent real harm to patients as a result of opioid therapy. Due to tolerance, dependence, and withdrawal, many patients taking prescription opioids today will require an enormous investment of resources to help them get off of opioids or onto lower, safer doses.
- g. Withdrawal refers to the physiologic manifestations of not having the substance, the symptoms of which vary from substance to substance. As a general albeit oversimplified principle, the characteristics of withdrawal from a given substance are the opposite of intoxication for that substance. Withdrawal from opioids includes dysphoria (unhappiness), anxiety, insomnia, agitation, restlessness, muscle fasciculations, increased heart rate, elevated blood pressure, diarrhea, nausea, vomiting, and body pain. Although opioid withdrawal is generally thought to be painful but not life threatening, people can die from opioid withdrawal, due to vital sign instability, suicide, and other complications.¹⁰⁸³
- h. Clinical experience and clinical studies demonstrate that the majority of opioid legacy chronic pain patients (that is, patients who have been taking opioids daily for months to years) are physiologically dependent on opioids and struggle to taper, even when opioids pose imminent risk.
 - i. In a study at Oregon Health & Sciences University, after a hospital and clinic wide policy was implemented to get high dose legacy patients' doses down below 120 MED per day, including intensive physician education from 2011 to 2013,¹⁰⁸⁴ 71 (63%) continued high-dose opioids in the post-intervention period.¹⁰⁸⁵ In other words, even with a hospital wide initiative, a minority of patients tapered to safer doses.
 - ii. In a Danish study in which subjects were tapered off of opioids by reducing by 10% of the daily opioid dose every week until discontinuation,¹⁰⁸⁶ only 13 of 35 patients randomized to the opioid taper completed the study without dropping out. The authors wrote "Although our study is hampered by a vast dropout rate, we still feel that it is highly

¹⁰⁸² Koob, "Neurocircuitry", fn. 40, above, at p. 217.

¹⁰⁸³ Stark MM, Payne-James J. People can die from opiate withdrawal. *Med Sci Law*. 2017;57(2):103. doi:10.1177/0025802417704600 at p. 103; *see also* Bohnert ASB, Valenstein M, Bair MJ, *et al.* Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA - J Am Med Assoc*. 2011;305(13):1315-1321, at p. 77.

¹⁰⁸⁴ Weimer MB, Hartung DM, Ahmed S, Nicolaidis C. A chronic opioid therapy dose reduction policy in primary care. *Subst Abus*. 2016;37(1):141-147, at pp. 141-142.

¹⁰⁸⁵ *Id.* at p. 114.

¹⁰⁸⁶ Kurita GP, Højsted J, Sjøgren P. Tapering off long-term opioid therapy in chronic non-cancer pain patients: A randomized clinical trial. *Eur J Pain*. 2018;22(8):1528-1543, at p. 1531.

justified to point to the fact that the stabilization of opioid treatment is not a simple task and opioid tapering off seems to be extremely difficult in CNCP patients in general”¹⁰⁸⁷

- i. The Pharmaceutical Opioid Industry consistently sought to downplay the importance of “dependence” on prescription opioids. As explained below, this effort included influencing the American Psychiatric Association’s change of the definitions of opioid-related disorders from the Diagnostic and Statistical Manual (DSM) IV to the DSM-5.
- j. On May 18, 2006, Purdue’s David Haddox received the “excellent news” from Sidney Scholl, of Pinney Associates, that “Chuck O’Brien will be heading up the SUD [Substance Use Disorder] section of the DSM-V. This means that there is a good chance that ‘addiction’ will replace ‘dependence’ and there can be some changes in the diagnostic criteria that will reflect issues related to abuse and addiction of prescription opioids. Chuck asked me to assist him in this process. I would appreciate your input in this process. . . . If Marc Schuckit, who was originally slated to head up the SUD section, was still in charge, we would not be in this position as he likes the use of dependence over addiction. This is an opportunity we should not overlook, as major revisions of the DSM do not occur very often.” Haddox wrote back, “This is really good news, Sid.”¹⁰⁸⁸
- k. On March 24, 2008, Haddox wrote to Phillipp Lippe in response to Lippe’s request for comments regarding the American Medical Association’s Report on Substance Abuse. Haddox wrote, “I am glad to see AMA getting into this area. Certainly the definitions and diagnostic criteria need some work...we are all fortunate that Charles O’Brien is the head of the substance use disorders section.”¹⁰⁸⁹
- l. On November 6, 2008, Haddox wrote to Chuck O’Brien, “It was good to see you this past weekend at ICPCD [International Conference on Pain and Chemical Dependency]. I really am excited that you are educating your nonclinical colleagues about the need for diagnostic nomenclature that are applicable in the real (read:clinical) world.” Haddox went on to ask O’Brien to consult on a tamper-resistant opioid analgesic work group, and referenced prior payment of \$2400 at O’Brien’s rate of \$600 per hour, “when it was anticipated that you would accompany us to the FDA Advisory Committee in March.” Haddox added, “Also, in the interest of public health and medicine, I don’t want to do anything to impair your ability to complete your DSM-V duties.” O’Brien wrote back on November 12, 2008, to “Dave, I would be very happy to do this but it would simplify my life with Penn if we could consider this activity an extension [of] my

¹⁰⁸⁷ *Id.* at p. 1536.

¹⁰⁸⁸ PPLP004058443.

¹⁰⁸⁹ PPLPC031000425439.

efforts of several months ago where I already signed a contract.” Haddox replied that he was “really pleased that you will be able to work with us on this.”¹⁰⁹⁰

- m. On March 25, 2008, Haddox again exchanged emails with Phillipp Lippe. Dr. Lippe expressed concern that under DSM-IV, the first three criteria for diagnosis of substance dependence “are inherent in pain management,” that is, “(1) Tolerance; (2) withdrawal symptoms; and (3) increased dosage or length of use.” Haddox wrote to Lippe, “I have great confidence that the DSM-V will improve on this language, based on the chair of the SUD [committee].”¹⁰⁹¹
- n. Dr. O’Brien’s consulting and financial relationship with Purdue goes back to at least 2003.¹⁰⁹² Through 2006, Dr. O’Brien appeared as an expert witness for Purdue in at least 9 cases in the federal courts of Florida, Missouri, Ohio, Texas, Georgia and Illinois and Texas state court¹⁰⁹³ providing opinions that plaintiffs were not addicted; not injured by dependence, which was described as an “expected consequence” of taking OxyContin and easily resolved by tapering.¹⁰⁹⁴ In the Savant v. Purdue case in 2005, Dr. O’Brien’s report stated that he was compensated at the rate of \$550 per hour.¹⁰⁹⁵ O’Brien signed a consulting agreement with Purdue, effective from April 2008-April 2013,¹⁰⁹⁶ essentially contemporaneous with his tenure as Chair of the DSM-5 Substance Abuse working group, from 2007-2013.¹⁰⁹⁷ Remarkably, in 2013, O’Brien disclosed no financial relationship to Purdue or any other party as a co-author and Chair of the group that published the rationale for the changes to the new DSM-5 section on substance abuse.¹⁰⁹⁸
- o. This sequence of events indicates that Purdue’s consultant, O’Brien, who was on a first name basis with Haddox, was responsible for the work that altered the

¹⁰⁹⁰ PPLPC018000252189 at -2190-2191.

¹⁰⁹¹ PPLPC018000201219 at -1219-1222.

¹⁰⁹² Dr. O’Brien testified that since 1969, he has been a paid consultant to numerous pharmaceutical/opioid manufacturers including McNeil, Janssen, Johnson & Johnson, Cephalon, Purdue and others. O’Brien also testified that he “helped them [McNeil] decide to purchase Tramadol from a German company and help them get that started.” Timmons v Purdue Pharma (2005) Deposition of Charles P. O’Brien, produced at PKY183320282 at -0393-0394.

¹⁰⁹³ Timmons v Purdue Pharma et al. No. 8:04-CV-1479-T-26MAP (M.D. Fla., 2005) produced at PKY183320282; Savant v Purdue Pharma et al., No. 04-394-DRH, 2005 WL 6503987 (S.D. Ill. 2005); Taylor v Purdue Pharma et al., No. 504-CV-197, 2005 WL 3308504 (M.D. Ga. 2005); McKnight v Purdue Pharma et al., No. 9:04 Civ-116, 2005 WL 5794391 (E.D. Tex. 2005); Harris v Purdue Pharma et al., No. C-1-01-428, 2004 WL 4012101 (S.D. Ohio 2004); Branch v Purdue Pharma et al. No. LR 1696-3, 2004 WL 3752789 (Tex. Dist. Richmond Civil); Campbell v Purdue Pharma et al, No. 1:02CV00163TCM, 2004 WL 6057307 (E.D. Mo. 2004); Labzda v Purdue Pharma et al., No. 01-8726-CIV-FERGUSONSNOW, 2003 WL 26100920 (S.D. Fla. 2003); Williams v Purdue Pharma et al., No. 4:04CV02407 (S.D. Tex. 2006), produced at PKY182921037

¹⁰⁹⁴ Harris, 2004 WL 4012101, at *5.

¹⁰⁹⁵ Savant, 2005 WL 6503987, at *9.

¹⁰⁹⁶ PPLP003478540

¹⁰⁹⁷ Hasin DS, O’Brien CP *et al.* DSM-5 Criteria for Substance Use Disorders: recommendations and rationale. *Am J Psychiatry* 2013;170(8):834-851. at p.2, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3767415/pdf/nihms515995.pdf>, at p. 2.

¹⁰⁹⁸ *Id.*, at pp. 1 and 12.

DSM-5 definition of opioid use disorder in a manner that suited Purdue's goals by distinguishing between "dependence" on the one hand, and "use disorder" or "addiction" on the other. This history is consistent with a larger effort on the part of Purdue and other opioid manufacturers to characterize dependence as a benign condition entirely separate from addiction. In reality, dependence, withdrawal, and tolerance, are closely linked to the disease of addiction, and from a neurobiological perspective, may be identical phenomena. Further, by excluding the criteria of tolerance and withdrawal, and by completely removing dependence from the diagnostic criteria, the DSM-5 raised the threshold for diagnosing OUD in this vulnerable population, consisting of approximately 25% of long-term opioid users who progressed to OUD.¹⁰⁹⁹ As a result of making it more difficult to diagnose OUD, some of these patients were denied the benefits of timely, evidence-based treatment of their conditions.

- p. Regardless of these changing and disparate definitions, the bottom line has not changed: prescription opioids induce physiological dependence almost universally, and result in addiction in a significant subset of users, particularly as dose and duration of exposure are increased. Both represent significant harms.
- q. Even limited exposure to opioids through a doctor's prescription, can lead to persistent opioid use. In other words, once patients start opioids, they are at significant risk to continue them beyond the time of injury, *i.e.* to become dependent on them.
 - i. Brummett *et al.* sought to determine the incidence of new persistent opioid use after minor and major surgical procedures. Using a nationwide insurance claims data set from 2013 to 2014, they calculated the incidence of persistent opioid use for more than 90 days among opioid-naïve patients after both minor and major surgical procedures. The authors found the rates of new persistent opioid use were similar between the two groups, ranging from 5.9% to 6.5%. By comparison, the incidence in the nonoperative control cohort was only 0.4%. The authors wrote, "New persistent opioid use represents a common but previously underappreciated surgical complication that warrants increased awareness."¹¹⁰⁰ The more opioids prescribed after surgery, the more patients tend to use. The number of opioid pain pills prescribed after surgery is a bigger predictor of how many opioids the patient will use, than is self-reported pain.
 - ii. A study by Delgado *et al.* looked at opioid naïve patients being treated for a common minor injury, ankle sprain, in the emergency department (ED) to determine the association between initial opioid prescription intensity

¹⁰⁹⁹ Vowles, "Rates of Opioid Misuse", fn. 847, above, discussed above at §C.8.b.

¹¹⁰⁰ Brummett CM, Waljee JF, Goesling J, *et al.* New persistent opioid use after minor and major surgical procedures in U.S. adults. *JAMA Surg.* 2017., at p. 1.

and transition to prolonged opioid use. The authors concluded that opioid prescribing for ED patients treated for ankle sprains is “common,” and prescriptions greater than 225 MED were associated with approximately five times higher rates of prolonged opioid use than with lower MED exposure. As the authors stated, “This is concerning because these prescriptions could still fall within 5- or 7-day supply limit policies aimed at promoting safer opioid prescribing.”¹¹⁰¹

- iii. A very recent 2020 retrospective cohort study of 259,115 opioid naïve adult patients undergoing endocrine surgery found the rate of new persistent opioid use [*i.e.*, receipt of 1 or more opioid prescriptions 90-180 days postop with no intervening procedures] was 7.4% but that “[i]mportantly, the risk for persistent opioid use increased with higher doses of total amount of opioids prescribed.”¹¹⁰²

■ Numerous other studies have been published in the last three years showing persistent opioid use 3-12 months after even minor surgeries in opioid naïve patients: (10%¹¹⁰³; 10%¹¹⁰⁴; 5%¹¹⁰⁵; 13%¹¹⁰⁶; 13%¹¹⁰⁷; 8%¹¹⁰⁸; 10%-13%¹¹⁰⁹)

- r. Conversely, the fewer opioids prescribed in the weeks and months following surgery, the less likely patients are to become persistent opioid users.¹¹¹⁰ When

¹¹⁰¹ Delgado, *et al.*, “National Variation,” fn. 1080, above, at p. 1

¹¹⁰² Kuo JH, et al. Use and Misuse of Opioids after Endocrine Surgery Operations. *Annals of Surgery*. 2020;1-6, at p. 1.

¹¹⁰³ Marcusa DP *et al.* Prescription Opioid Abuse among Opioid-Naïve Women Undergoing Immediate Breast Reconstruction. *Plast Reconstr Surg*. 2017 Dec;140(6):1081-1090. doi: 10.1097/PRS.0000000000003832, at p. 1081.

¹¹⁰⁴ Lee JS *et al.* New Persistent Opioid Use Among Patients with Cancer after Curative-Intent Surgery. *J Clin Oncol*. 2017 Dec 20;35(36):4042-4049. doi: 10.1200/JCO.2017.74.1363, at p. 4042.

¹¹⁰⁵ Harbaugh, *et al.*, “Persistent Opioid Use”, fn. 1056, above, at p. 1.

¹¹⁰⁶ Deyo RA *et al.* Use of Prescription Opioids Before and After an Operation for Chronic Pain (lumber fusion surgery). *Pain*. 2018 Jun;159(6):1147-1154. doi: 10.1097/j.pain.0000000000001202, at p. 5.

¹¹⁰⁷ Johnson SP *et al.* Risk of Prolonged Opioid Use Among Opioid-Naïve Patients Following Common Hand Surgery Procedures. *J Hand Surg Am*. 2016 Oct;41(10):947-957.e3. doi: 10.1016/j.jhsa.2016.07.113, at p. 947.

¹¹⁰⁸ Goesling J *et al.* Trends and Predictors of Opioid Use After Total Knee and Total Hip Arthroplasty. *Pain*. 2016 Jun;157(6):1259-65. doi: 10.1097/j.pain.0000000000000516, at p. 1259.

¹¹⁰⁹ Cook DJ *et al.* Benchmarks of Duration and Magnitude of Opioid Consumption After Total Hip and Knee Arthroplasty: a database analysis of 69,368 patients. *J Arthroplasty*. 2019; 34: 638-644, at p. 638.

¹¹¹⁰ Brummett, “New Persistent Opioid Use”, fn. 1100, above; Gil JA, *et al.* Risk of Prolonged Opioid Use Among Opioid-Naïve Patients After Common Shoulder Arthroscopy Procedures. *Am J Sports Med* 2019; 47(5); 1043-1050, at p. 1049; Larach DB, Sahara MJ, *et al.* Patient Factors Associated with Opioid Consumption in the Month Following Major Surgery. *Ann Surg*. 2019; 1-9, at p. 1.

opioids are restricted, patients do not tend to experience more pain, less satisfaction, or call in more frequently for refills.¹¹¹¹

- s. A recent NASEM Report addresses the role of opioid prescribing for acute pain, including surgical and other contexts, as a contributing factor to the epidemic of abuse, overdose and mortality.¹¹¹² The Report confirms the increasing awareness that opioids are overprescribed even for acute pain, and that an important subset of acute pain patients go on to long-term use of prescription opioids and the risks that accompany such use.¹¹¹³
- t. Just as increased exposure has been the cause of increased consumption and risk,¹¹¹⁴ decreasing exposure decreases opioid consumption and risk. When doctors initiate fewer opioids, patients consume fewer opioids, without increases in pain. Limiting opioid prescribing is good medicine, because it decreases exposure to a dangerous and potentially lethal drug, without compromising pain treatment, while at the same time reducing the risk of diversion of unused pills to unauthorized users. Recent studies in a wide range of medical conditions have consistently demonstrated that patients' experience of pain is not increased when opioids are reduced or eliminated from treatment protocols. Examples of research are summarized below.
 - i. In a study in which patients were treated with Tylenol/ibuprofen after parathyroid and thyroid surgery, the authors concluded that such patients "need very little, if any, post-operative opioids....Decreasing the volume of opioid medications prescribed at discharge will decrease waste and reduce potential for addiction."¹¹¹⁵

¹¹¹¹ Bateman BT, Cole NM, *et al.* Patterns of opioid prescription and use after cesarean delivery. *Obstet Gyn.* 2017; 130(1): 1-17, at p. 3; Howard R, *et al.* Reduction in opioid prescribing through evidence-based prescribing guidelines. *JAMA Surg* 2018; 153(3): 285-287, at p. 287; Lee JS, Hu HM, Brummett CM, *et al.* Postoperative Opioid Prescribing and the Pain Scores on Hospital Consumer Assessment of Healthcare Providers and Systems Survey. *JAMA.* 2017;317(19):2013–2015, at p. 2014; Sekhri S, Arora NS, *et al.* Probability of opioid prescription refilling after surgery: does initial prescription dose matter? *Ann Surg.* 2018; 268(2): 271-276, at p. 275.

¹¹¹² National Academies of Sciences, Engineering, and Medicine (NASEM 2020). 2020. *Framing Opioid Prescribing Guidelines for Acute Pain: Developing the Evidence*. Washington, DC: The National Academies Press. <https://www.nap.edu/catalog/25555/framing-opioid-prescribing-guidelines-for-acute-pain-developing-the-evidence>

¹¹¹³ *Id.*, at p. 1. A further, very recent publication adds to this evidence: among women who took prescription opioids for acute pain after childbirth, there was an increased risk of Serious Opioid-Related Events (a composite consisting of persistent opioid use, opioid use disorder diagnosis, methadone or buprenorphine prescription, opioid overdose diagnosis, and opioid-related death) compared with women who did not take opioids after childbirth, and the risk increased with more post-partum opioid prescriptions. Osmundson SS, *et al.*, Opioid prescribing after childbirth and risk for serious opioid-related events: a cohort study. *Annals of Internal Medicine* 2020; doi:107326/M19-3805, at p. 2.

¹¹¹⁴ Howard, *et al.*, "Association of Opioid Prescribing," fn. 1080, above, at p. E6.

¹¹¹⁵ Shindo M, Lim J, Leon E, Moneta L, Li R, Quintinalla-Diek L. Opioid Prescribing Practice and Needs in Thyroid and Parathyroid Surgery. *JAMA Otolaryngology - Head and Neck Surgery.* 2018, at p. 1102.

- ii. A case-control cohort study of 1,231 patients undergoing gynecologic oncology surgery, implemented an “ultrarestrictive opioid prescription protocol” (UROPP), resulting in a significant decrease in the number of opioids dispensed during the entire perioperative period, without changes in postoperative pain scores, complications, or increases in the number of refill requests.¹¹¹⁶
- iii. The authors write, “For patients who underwent laparoscopic or robotic surgery, the mean (SD standard deviation) number of opioid tablets given at discharge was 38.4 (17.4) before implementation of the UROPP and 1.3 (3.7) after implementation ($P < .001$). After ambulatory surgery, the mean (SD) number of opioid tablets given at discharge was 13.9 (16.6) before implementation of the UROPP and 0.2 (2.1) after implementation ($P < .001$). The mean (SD) perioperative oral morphine equivalent dose was reduced to 64.3 (207.2) mg from 339.4 (674.4) mg the year prior for all opioid-naïve patients ($P < .001$).”¹¹¹⁷
- iv. “The significant reduction in the number of dispensed opioids was not associated with an increase in the number of refill requests (104 patients [16.6%] in the pre-UROPP group vs 100 patients [16.5%] in the post-UROPP group; $P = .99$), the mean (SD) postoperative visit pain scores (1.1 [2.2] for the post-UROPP group vs 1.4 [2.3] for pre-UROPP group; $P = .06$), or the number of complications (29 cases [4.8%] in the post-UROPP group vs 42 cases [6.7%] in the pre-UROPP group; $P = .15$).”¹¹¹⁸
- v. Similarly, non-opioids have been found equivalent to opioids for relief of pain treated in emergency departments. “For adult ED [Emergency Department] patients with acute extremity pain, there were no clinically important differences in pain reduction at 2 hours with ibuprofen and acetaminophen or 3 different opioid and acetaminophen combination analgesics.”¹¹¹⁹ Based on data from 2006-2010, opioids were prescribed for 18.7% of ED discharges; yet “[t]he findings support the inference that there are no clinically meaningful differences between the analgesic effects of these 4 analgesics and suggest that a combination of ibuprofen and acetaminophen represents an alternative to oral opioid analgesics for

¹¹¹⁶ Mark J, Argentieri DM, Gutierrez CA, *et al.* Ultrarestrictive Opioid Prescription Protocol for Pain Management After Gynecologic and Abdominal Surgery. *JAMA Netw Open*. 2018;1(8):e185452. doi:10.1001/jamanetworkopen.2018.5452.

¹¹¹⁷ *Id.* at p. 1.

¹¹¹⁸ *Id.* at pp. 1-2.

¹¹¹⁹ Chang AK, *et al.* Effect of a Single Dose of Oral Opioid and Nonopioid Analgesics on Acute Extremity Pain in the Emergency Department: A Randomized Clinical Trial. *JAMA*. 2017;318(17):1661–1667. doi:10.1001/jama.2017.16190, at p.1661.

the treatment of acute extremity pain in the ED.”¹¹²⁰

- u. In most cases, opioid dependent patients require a protracted medically supervised taper to lower their doses. I have worked with others to develop a protocol for safely and compassionately tapering opioid-dependent patients to lower doses or to eliminate them entirely. *See* discussion of the “BRAVO Protocol” and my recent publication on patient-centered tapering, below. Studies show that pain in the majority of patents *improves* when patients on chronic high dose opioid therapy reduce their dose or come off of opioids.
- v. It is inhumane to abruptly discontinue opioids in patients who have become dependent through a medical prescription.¹¹²¹ The preferred approach is a slow and compassionate taper¹¹²² when risks outweigh the benefits.
- w. A retrospective research study of patients consecutively admitted to the Mayo Clinic Pain Rehabilitation Center from 2006 through 2012, with a pain diagnosis of fibromyalgia, showed that patients tapered off of opioids had significant improvements in pain-related measures including numeric pain scores and functionality.¹¹²³
- x. A meta-analysis of opioid legacy patients (patients on long-term opioid therapy as a “legacy” of opioid prescribing in the 1990s) demonstrated that pain improves for many patients who decrease or go off of long-term opioid therapy (LTOT). Sixty-seven studies were included in this analysis. Among 40 studies examining patient outcomes after dose reduction, improvement was reported in pain severity (8 of 8 fair-quality studies), function (5 of 5 fair-quality studies), and quality of life (3 of 3 fair-quality studies).¹¹²⁴ The authors repeatedly note the need for more research and better quality evidence. Nonetheless, the authors concluded, “this systematic review suggests that pain, function and quality of life may improve during and after opioid dose reduction.”¹¹²⁵
- y. In a study by Sullivan *et al.*, high dose legacy patients were randomly assigned to a 22-week taper support intervention (psychiatric consultation, opioid dose tapering, and 18 weekly meetings with a physician assistant to explore motivation

¹¹²⁰ *Id.*

¹¹²¹ United States Department of Health and Human Services. *HHS Guide for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-term Opioid Analgesics*. (Oct. 2019); https://www.hhs.gov/opioids/sites/default/files/2019-10/Dosage_Reduction_Discontinuation.pdf.

¹¹²² *Id.* at p. 3, opioid tapering flowchart based on Oregon Pain Guidance BRAVO protocol.

¹¹²³ Cunningham JL, Evans MM, King SM, Gehin JM, Loukianova LL. Opioid tapering in fibromyalgia patients: Experience from an interdisciplinary pain rehabilitation program. *Pain Med* (United States). 2016. doi:10.1093/pm/pnv079, at p. 1676.

¹¹²⁴ Frank JW, Lovejoy TI, Becker WC, *et al.* Patient outcomes in dose reduction or discontinuation of long-term opioid therapy: A systematic review. *Ann Intern Med*. 2017;167(3):181-191. doi:10.7326/M17-0598, at pp. 185-186.

¹¹²⁵ *Id.* at p. 186.

for tapering and learn pain self-management skills) or usual care (N=35).¹¹²⁶ The authors write, “It is important to note that the opioid dose reduction in both the taper support and usual care groups was achieved without a significant increase in pain severity. In fact, pain severity decreased on average from baseline to 22 weeks by approximately 1 point on the 0-10 scale in the taper support group and approximately a half-point in the usual care group. This finding is consistent with those in studies of inpatient pain rehabilitation programs, which have documented pain reduction with opioid dose reduction.”¹¹²⁷

- z. A small outpatient study of opioid tapering in community patients showed no increase in pain intensity scores in patients who were able to taper their opioids by greater than 50% from the starting dose. The median opioid dose in the sample was 288 MED. The median duration of opioids was six years. Median pain intensity was moderate (5 out of 10 on a numeric pain rating). After four months, the median MED was reduced to 150 (IQR, 54-248) mg (P = .002). Of note, neither pain intensity (P = .29) nor pain interference (P = .44) increased with opioid reduction.¹¹²⁸
- aa. Many patients on chronic opioid therapy are reluctant to taper. In addition, some physicians and authors question whether tapering is necessary if the patient is stable and adherent to their current dose. Yet it is well established that patients on high doses of opioids are at increased risk for a variety of side effects, serious morbidities, and death.¹¹²⁹ Quality of life may be adversely affected, despite the fact that the patient perceives benefit in terms of pain relief. Indeed, as above, data show that in addition to reducing opioid-related risk, pain can improve when patients lower their opioids, which is evidence in and of itself that opioids do not work for chronic pain for those patients.
- bb. A newborn is born dependent on opioids as a result of being exposed to opioids *in utero*. According to DSM-5 criteria, the opioid dependent newborn is not “addicted,” because addiction requires the manifestations of certain pathological and maladaptive behaviors in conjunction with opioid use. The newborn is the passive recipient of opioids due to the mother’s exposure.

¹¹²⁶ Sullivan MD, Turner JA, DiLodovico C, D’Appollonio A, Stephens K, Chan Y-F. Prescription Opioid Taper Support for Outpatients With Chronic Pain: A Randomized Controlled Trial. *J Pain*. 2017. doi:10.1016/j.jpain.2016.11.003, at p. 308.

¹¹²⁷ *Id.* at p. 318.

¹¹²⁸ Darnall BD, Ziadni MS, Stieg RL, Mackey IG, Kao MC, Flood P. Patient-centered prescription opioid tapering in community outpatients with chronic pain. *JAMA Intern Med*. 2018. doi:10.1001/jamainternmed.2017.8709, at p. 708.

¹¹²⁹ Gomes T, Mamdani MM, Dhalla Ia, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med*. 2011;171(7):686-691. doi:10.1001/archinternmed.2011.117, at p. 686; see also Lembke *et al.*, Weighing The Risks,” fn. 4, above, at p. 982; Edlund *et al.*, Role of Opioid Prescription,” fn. 76, above, at p. 7; Chou *et al.*, “Effectiveness and Risks,” fn. 308, above, at p. ES-1.

- i. The rate of admission to neonatal intensive care units (“NICU”) for neonatal abstinence syndrome (“NAS”), a drug-withdrawal syndrome that occurs after in utero exposure to opioids, increased from 7 cases per 1000 admissions to 27 cases per 1000 admissions between 2004 and 2013.¹¹³⁰
- ii. Tolia reported that “the median length of stay increased from 13 days to 19 days ($P < 0.001$ for both trends). The total percentage of NICU [neonatal intensive care unit] days nationwide that were attributed to the neonatal abstinence syndrome increased from 0.6% to 4.0% ($P < 0.001$ for trend), with eight centers reporting that more than 20% of all NICU days were attributed to the care of these infants in 2013.”¹¹³¹
- iii. This approximate quadrupling of the rate of NAS is directly attributable to the epidemic of opioid use disorder that began with promotion of prescription opioids and continues to the present, accompanied by use of illicit opioid drugs.
- cc. Defendants’ promotional documents conveyed the message that prescription opioid dependence is not a significant concern, and that patients can be easily tapered off their prescriptions in a brief period of time. That message is contradicted by the scientific literature, my own clinical experience, and patients’ own accounts.¹¹³² This messaging improperly contributed to physicians’ false sense of security in the belief that prescription opioids can be prescribed without substantial risk. (*See* Appendix I). Further, misleading statements by Defendants on the efficacy of opioids in the treatment of chronic pain (*see* Appendix I) are inconsistent with the medical evidence that pain improves in many chronic pain patients who are tapered down and/or off of opioids.

11. Increased supply of prescription opioids contributed substantially to diversion of prescription opioids to individuals for whom they had not been prescribed (The Tsunami Effect).

- a. As stated in the 2013 CDC Report: “Almost all prescription drugs involved in abuse come from prescriptions originally. However, once they are prescribed and dispensed, prescription drugs are frequently diverted to people using them without prescriptions. There are instances where pharmacies are dispensing large quantities of opioids as part of an illegal distribution scheme as well as

¹¹³⁰ Tolia VN, Patrick SW, Bennett MM, *et al.* Increasing incidence of the neonatal abstinence syndrome in U.S. neonatal ICUs. *Obstet Gynecol Surv.* 2015. doi:10.1097/OGX.0000000000000243, at p. 2118.

¹¹³¹ *Id.* at p. 2118.

¹¹³² Rieder TN. In opioid withdrawal, with no help in sight. *Health Aff.* 2017;36(1):182-185. doi:10.1377/HLTHAFF.2016.0347

pharmacists who fail to meet their obligation to determine that a prescription was issued for a legitimate medical purpose.”¹¹³³

- b. This quote highlights the large role that diversion of prescription opioids has played in the current epidemic. In addition to people getting addicted to and being harmed by opioids prescribed directly to them, millions have been harmed through diversion of prescription opioids to unauthorized sources, from teenagers experimenting to people already addicted to opioids gaining easier access through the illicit market.
- c. An efficient distributor supply chain enabled opioid manufacturers to make prescription opioids available on a mass scale to large numbers of people in rural and remote settings, as well as urban and suburban settings, expanding both the licit and illicit drug market, and setting this opioid epidemic apart from prior epidemics and other drug epidemics. The sheer scale of access to opioids made possible through the distribution and supply chain, led individuals who otherwise would never have been exposed, to use and subsequently be killed or harmed by opioids.¹¹³⁴
- d. As stated in a recent NASEM report, “the increase in the availability of drugs and both the long-term and increasing vulnerability of these population groups combined to create and fuel the rising trend in drug poisoning deaths. The country’s drug overdose crisis represents a ‘perfect storm’ of the flooding of the market with highly addictive yet deadly substances and underlying U.S. demand for and vulnerability to substances that temporarily numb both physical and mental pain.”¹¹³⁵
- e. It is important to recognize that although many of the communities hit hardest by the opioid epidemic were already struggling with serious social and economic problems, the sudden availability of and easy access to opioids, initially in prescription pill form, contributed to the economic and social devastation of many towns across America.¹¹³⁶ Economic downturn and the efflux of manufacturing jobs in towns across America in the last thirty years, have contributed to so-called “deaths of despair” – early mortality in middle aged non-Hispanic whites due primarily to drug overdose.¹¹³⁷ Nonetheless, economic disadvantage contributes

¹¹³³ United States Department of Health and Human Services. Addressing Prescription Drug Abuse in the United States. :1-36, at p. 16. *See*

https://www.cdc.gov/drugoverdose/pdf/hhs_prescription_drug_abuse_report_09.2013.pdf.

¹¹³⁴ *See also* § C.2.i.iii, above, re likely extent of diversion of prescription opioids.

¹¹³⁵ NASEM 2021, fn. 91, above, at p. 7-19.

¹¹³⁶ Ruhm CJ. Deaths of Despair or Drug Problems? NBER Working Paper No. 24188, NBER Program(s):Health Care, Health Economics, Public Economics, *National Bureau of Economic Research, Inc.* (2017).

¹¹³⁷ Case A, Deaton A. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. *Proc Natl Acad Sci.* 2015. doi:10.1073/pnas.1518393112, at p. 15081.

only 10-20% of mortality risk attributable to opioids, whereas the larger share of risk is due to supply of opioids in a given geographic region.¹¹³⁸

- f. ARCOS data on opioid prescribing show a 9% increase in opioid-related hospitalizations for each one morphine kilogram equivalent increase in opioid sales at the county level.¹¹³⁹ These data demonstrate a clear and convincing relationship between opioid dispensing and opioid related harm.¹¹⁴⁰
- g. Khan *et al.*, writing in *JAMA Internal Medicine* in 2019, show that an opioid prescription to one family member increases the risk of opioid overdose death to others in the same family, even though they do not have an opioid prescription. This study identifies 2,303 individuals who experienced opioid overdose and 9,212 matched control individuals, and shows that any prior opioid dispensing to family members was associated with overdose (odds ratio [OR], 2.89 [95% CI, 2.59-3.23]) in other family members. Risk of overdose increased in a dose-response fashion: Odds of overdose (>0-<50 morphine milligram equivalents per day: OR, 2.71 [95% CI, 2.42-3.03]; 50-<90 morphine milligram equivalents per day: OR, 7.80 [95% CI, 3.63-16.78]; ≥90 morphine milligram equivalents per day: OR, 15.08 [95% CI, 8.66-26.27]).¹¹⁴¹
- h. A 2021 study examining parents prescribed opioids for medical conditions found that their adolescent children are more likely to be prescribed opioids as well as misuse prescription opioids. The study found that “controlling for other factors, parental medical prescription opioid use was associated with adolescent prescription opioid medical use (adjusted odds ratio [aOR] 1.28; 95% CI, 1.06-1.53) and misuse (aOR. 1.53; 95% CI, 1.07-2.25), whereas parental misuse was not.”¹¹⁴² The authors found that “the association of parental medical prescription opioid use with adolescent prescription opioid misuse suggests that role modeling and availability of parents’ opioid medications in the household are significant familial risk factors for prescription opioid misuse among young people, although adolescents also misuse their own prescription opioid medications and prescriptions opioids from nonfamilial sources.”¹¹⁴³
- i. A study of US 12th grade adolescents found that students attending schools with the highest rates of medical use of prescription opioids had a 57% increased odds of prescription opioid misuse, compared with schools that had no medical use of

¹¹³⁸ Ruhm, *et al.*, “Deaths of Despair,” fn. 1136, above.

¹¹³⁹ Ghertner R. U.S. County Prevalence of Retail Prescription Opioid Sales and Opioid-Related Hospitalizations from 2011 to 2014. *Drug and Alcohol Dependence* 194 (2019):330–335, at p. 330.

¹¹⁴⁰ *Id.* at p. 333.

¹¹⁴¹ Khan NF, Bateman BT, *et al.* Association of Opioid Overdose with Opioid Prescription to Family Members. *JAMA Intern Med.* doi:10.1001/jamainternmed.2019.1064, at p. E3.

¹¹⁴² Griesler PC, *et al.* Assessment of prescription opioid medical use and misuse among parents and their adolescent offspring in the US. *JAMA Network Open.* 021;4(1):1-16, at p. 1.

¹¹⁴³ *Id.*, at p. 11.

prescription opioids.¹¹⁴⁴ “The robust association between school-level medical use of prescription opioids and POM [prescription opioid misuse] is consistent with evidence showing the largest sources of prescription opioids among adolescents are peers and leftover medication.”¹¹⁴⁵ The authors state that this association has weakened in recent years, which may be due to the impact of efforts to reduce prescription opioid misuse, or because adolescents “are turning to more readily available substances (e.g., marijuana, heroin) as prescription opioids become less available.”¹¹⁴⁶

- j. The recent NASEM report on guidelines for opioid use for acute pain (NASEM 2020), referenced above, further states that “Opioids pose risks not only to the patients for whom they are prescribed, but also to family members and to the community. Unused opioid pills from opioid prescriptions can be diverted to family members and friends (Bicket et al., 2019; Hill et al., 2017; Howard et al., 2019; Thiels et al., 2017). These unused pills, which often are not disposed of properly, may be used by the patient for indications other than those for which they were prescribed (e.g., as a sleep aid), or they may be used by someone other than the patient (Bicket et al., 2017; Jones et al., 2014). Individuals with opioid use disorder commonly report that they started by misusing prescription opioids (Ali et al., 2019; Becker et al., 2008; Cicero et al., 2014; NASEM, 2019). Furthermore, there is an association between the size of a patient’s opioid prescription and the likelihood of an opioid overdose among the patient’s family members (Khan et al., 2019). This association is present in children and adolescents as well as in adults (Khan et al., 2019). Among individuals who misuse prescription opioids, the most common source of opioids was pills from family members and friends. Among individuals who use heroin, the majority (66%) previously misused prescription opioids (Cicero et al., 2014). *Thus, opioid overprescribing, that is, prescribing more opioids than are necessary to control a patient’s acute pain, is a factor contributing to the public health epidemic of opioid overdoses.*”¹¹⁴⁷
- k. Opioid overprescribing after surgery is a significant contributor to the Tsunami Effect. A recent study reported that 83% of US patients who reported no pain after operation were discharged on opioids compared with 8.7% of non-US patients (p<0.001).¹¹⁴⁸ After discharge, the number of opioid prescription refills was substantially higher among US patients compared with non-US patients (7.1% vs 0.1%; p<0.001).¹¹⁴⁹ US patients were also prescribed more pills in

¹¹⁴⁴ McCabe SE, et al. Medical use and misuse of prescription opioids in US 12th grade youth: School-level correlates. *Pediatrics*. 2020;146(4):1-13, at p. 1.

¹¹⁴⁵ *Id.*, at p. 8.

¹¹⁴⁶ *Id.*, at p. 9.

¹¹⁴⁷ NASEM 2020, fn. 1112, above, at pp. 15-16 (emphasis added).

¹¹⁴⁸ El Moheb M, et al. Pain or No Pain, We Will Give You Opioids: Relationship between number of opioid pills prescribed and severity of pain after operation in U.S. vs non-U.S. patients. *J Am Coll Surg*. 2020;231(6):639-648, at p. 642-644.

¹¹⁴⁹ *Id.*, at p. 642.

higher doses than their non-US counterparts. The mean adjusted OME [oral morphine equivalent] and number of pills for US patients increased from 156.1 OME and 20.6 pills in US patients without pain, to 213.4 OME and 27.1 pills in US patients with severe pain, compared to non-US prescribing of 9.8 OME and 1.4 pills in non-US patients without pain and 26.8 OME and 4.5 pills in non-US patients with severe pain.¹¹⁵⁰ The authors state that “The large quantity of unused pills increases the risk of opioid misuse and diversion to the community at large.”¹¹⁵¹ The frequent and completely unnecessary prescription of powerful and addictive drugs to patients who are not experiencing any degree of pain is emblematic of the extent to which the Defendants’ false messages of prescription opioid safety, and their ubiquitous distribution, have permeated the medical profession and continue to exert their harmful influence.

1. Finally, an objective observer would have appreciated that the number of opioid pills being shipped to pharmacies all over the United States, including the state of Ohio, was far in excess of medical need. Annual Production Quotas (APQs) that were approved by the DEA, despite FDA recommendations for lower amounts, were based on unsupported Industry claims of market demand, without consideration of the obvious concern that the requested APQs included substantial diversion that contributed to the prescription opioid epidemic. While the DEA bears some responsibility for routinely accepting sales figures and unsupported claims of increased demands as a proxy for legitimate needs,¹¹⁵² the Industry itself bears primary responsibility for submitting requests for APQs that “were clearly excessive from 2010-2016.”¹¹⁵³

12. The increased supply of prescription opioids through licit and illicit sources resulted in a prescription opioid epidemic in the United States. “Epidemic,” defined as an outbreak of disease that spreads quickly and affects many individuals at the same time, is the appropriate term to describe the increase in opioid related morbidity and mortality beginning in the 1990’s and continuing to the present day.

- a. The societal effects of this opioid epidemic are worse than the societal effects of other drug epidemics, because of the accelerated devastation to individuals and communities, including (i) high rates of addiction and death in young people in the prime of their lives;¹¹⁵⁴ (ii) high rates of pregnant women being exposed to

¹¹⁵⁰ *Id.*, at p. 643.

¹¹⁵¹ *Id.*, at p. 646.

¹¹⁵² State of West Virginia Office of the Attorney General, “DEA’s Failure to Combat Diversion Cost Lives: results from the West Virginia Attorney General’s Investigation into the DEA’s catastrophic failure to manage the National Drug Quota System from 2010-2016, (June 4, 2020), at p. 29

¹¹⁵³ *Id.*, at p. ES-4.

¹¹⁵⁴ The Kaiser Family Foundation State Health Facts; Opioid Overdose Deaths by Age Group (1999-2018), <https://www.kff.org/other/state-indicator/opioid-overdose-deaths-by-age-group/?dataView=1&activeTab=graph¤tTimeframe=0&startTimeframe=19&selectedDistributions=25-34--35-44--total&selectedRows=%7B%22states%22:%7B%22ohio%22:%7B%7D%7D%7D&sortModel=%7B%22colId%22:%7B%22Location%22,%22sort%22:%22asc%22%7D> (last accessed Dec. 21, 2020). From 2000 through 2018, the total

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opioids and giving birth to babies dependent on opioids, who in turn suffer long-term cognitive consequences;¹¹⁵⁵ (iii) the tragic disruption to families and communities due to loss of parental caregivers,¹¹⁵⁶ requiring substantial resources for foster care; and (iv) exodus from the work force as a result of opioid dependence and addiction.¹¹⁵⁷

i. Long-term effects of Prenatal Opioid Exposure (“POE”)

- A. In a recent *JAMA* meta-analysis, the authors reported statistically significant cognitive and motor deficits among children exposed to prenatal opioids compared to unexposed children, from birth through age 6; deficits found among children from age 7-18 were no longer statistically significant.¹¹⁵⁸ The authors stated, “The cause and association of this with POE or other factors (*e.g.*, withdrawal treatment) are uncertain but suggest that POE necessitates long-term support and intervention.”¹¹⁵⁹ It should be noted that, to the extent that “withdrawal treatment” may be a cause of the observed deficits, such treatment itself would not have been required if not for the POE that precipitated the withdrawal and accompanying need for treatment. Further, “children with POE are 3 times more likely to have severe intellectual disability according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition criteria Poor neurodevelopmental outcomes in children with POE, even from an early age, is not novel information. However, our data appear to indicate that neurodevelopment did not improve after preschool and worsened by school age.”¹¹⁶⁰
- B. Similar results were reported in a study of the academic testing of Australian children who had been diagnosed with NAS at birth. Test scores of NAS children were compared to those of matched

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number of Ohio opioid overdose deaths were greatest between the ages of 25-34 (7,088 deaths) and 35-44 (6,972 deaths).

¹¹⁵⁵ Yeoh SJ, *et al.* Cognitive and motor outcomes of children with prenatal opioid exposure: a systemic review and meta-analysis. *JAMA Network Open*. 2019; 2(7): 1-14, at pp. 1-2.

¹¹⁵⁶ Radel L, Baldwin M, *et al.* Substance use, the opioid epidemic, and the child welfare system: key findings from a mixed methods study. *ASPE Research Brief*. (March 7, 2018)

¹¹⁵⁷ Franklin GM, *et al.* Early opioid prescription and subsequent disability among workers with back injuries. *Spine*. 2008; 33(2): 199-204; *see also* Anora M. Gaudiano, *How the opioid epidemic is exacerbating a US labor-market shortage*. MarketWatch, June 29, 2018. <https://www.marketwatch.com/story/how-the-opioid-epidemic-is-exacerbating-a-us-labor-market-shortage-2018-06-28>.

¹¹⁵⁸ Yeoh, “Cognitive and Motor Outcomes”, fn. 1155, above.

¹¹⁵⁹ *Id.*, at p. 2.

¹¹⁶⁰ *Id.*, at pp. 8-9.

controls and the general population, at Grades 3, 5, 7, and 9, which correspond to ages 8-9, 10-11, 12-13, and 14-15, respectively. The authors reported, “Our results show that a diagnosis of NAS is associated with poorer performance in standardized and compulsory curriculum-based tests from as early as 8 or 9 years of age in grade 3 of school when compared with other NSW [New South Wales] children, including those who were matched for gender, gestation, and socioeconomic status. Indeed, by the first year of high school, children with NAS performed even more poorly than other children in grade 5 who were, on average, 2 years younger. By grade 7, 44% of children with NAS had failed to meet NMS [National Minimum Standards] in ≥ 1 domain of testing.”¹¹⁶¹

- C. While noting that the cause for these effects is “uncertain,” the authors cited known biological mechanisms that could reasonably explain the deficits: “NAS is caused by transplacental exposure to drugs of addiction or dependency that interfere with brain function and development. Opioids impair adult brain function and cognitive skills even after only a few days of use, and their effects on the developing brain are subtle but long-lasting and include alterations to neuronal apoptosis, dendritic morphogenesis, and neurotransmitter homeostasis.”¹¹⁶² Further, the risk of failure to meet NMS (OR=2.5) was greater for NAS than for any other risk factor investigated.¹¹⁶³
- D. The consistency of results from the Yeoh and Oei studies provides support for the conclusion that NAS contributes substantially to persistent developmental deficits. “This finding is of great concern because school failure increases the risk of myriad poor adult outcomes, including depression in women, criminal activity, and drug use. We showed that children with NAS performed more poorly in all 5 test domains, including reading or literacy skills, 1 of the most important predictors of school success. Children who cannot read at expected levels by grade 3 are less likely to enroll in college or graduate high school. In the United Kingdom, two-thirds of prisoners have a reading age <11 years. Furthermore, test results in children with NAS worsened as they entered high school.”¹¹⁶⁴

¹¹⁶¹ Oei JL, *et al.* Neonatal Abstinence Syndrome and High School Performance. *Pediatrics*. 2017;139(2):e20162651, at p. 7.

¹¹⁶² *Id.*

¹¹⁶³ *Id.*

¹¹⁶⁴ *Id.*

- E. A recent study found developmental delays among infants exposed to opioids in utero, even where the newborns displayed no overt symptoms of NAS. The authors reported, “Compared to infants with no detected exposures the diagnosis of developmental delay was highest among infants with NAS (7.6% versus 28.3%). However, the diagnosis was still twice as likely among opioid exposed infants without NAS (7.6% versus 15.6%).”¹¹⁶⁵
- ii. Loss of Parental Caregivers and Impacts on Foster Care: A 2018 study of the relationship between drug use and foster care reported, “Higher rates of overdose deaths and drug hospitalizations correspond with higher child welfare caseload rates. We estimate that in the average county nationwide, a 10 percent increase in the overdose death rate corresponded to a 4.4 percent increase in the foster care entry rate. Similarly, a 10 percent increase in the average county’s drug-related hospitalization rate corresponded to a 2.9 percent increase in its foster care entry rate.”¹¹⁶⁶ While the increased rates of overdose deaths are not exclusively linked to opioids, data cited previously support the significantly greater share of drug mortality attributable to opioids than to other drugs.¹¹⁶⁷
- Exodus from the workforce: It is well-known that widespread distribution and use of opioids has had a significant adverse effect on the availability of workers, both due to increased mortality and the myriad problems associated with opioid use. According to a recent analysis, “The opioid epidemic is preventing a huge portion of the population that is sidelined from joining the labor force because labor intensive jobs are also the ones that require workers who can pass drug tests.”¹¹⁶⁸ The opioid epidemic is responsible for this detrimental impact. Franklin (2008) found that “receipt of opioids for more than 7 days (odds ratio 2.2; 95% confidence interval, 1.5-3.1) and receipt of more than 1 opioid prescription were associated significantly with work disability at 1 year.” Another study of long-term opioid use and opioid use disorder among construction workers found that “workers prescribed long-term opioids in any calendar quarter had a

¹¹⁶⁵ Hall ES *et al.* Developmental disorders and medical complications among infants with subclinical intrauterine opioid exposures. *Population Health Management*. 2019;22;19-24, at p. 21.

¹¹⁶⁶ Radel, “Child Welfare System”, fn. 1156, above, at pp. 2-3.

¹¹⁶⁷ See, e.g., Centers for Disease Control and Prevention, *Opioid Overdose*, <https://www.cdc.gov/drugoverdose/index.html>: “Drug overdose deaths continue to increase in the United States. From 1999 to 2017, more than 702,000 people have died from a drug overdose. In 2017, more than 70,000 people died from drug overdoses, making it a leading cause of injury-related death in the United States. Of those deaths, almost 68% involved a prescription or illicit opioid.” (emphasis added).

¹¹⁶⁸ Anora M. Gaudiano, *How the Opioid Epidemic Is Exacerbating a US Labor-Market Shortage*, MarketWatch (June 29, 2018), <https://www.marketwatch.com/story/how-the-opioid-epidemic-is-exacerbating-a-us-labor-market-shortage-2018-06-28>.

nearly 10-fold odds of developing an OUD.”¹¹⁶⁹ An additional study of labor force loss due to opioids estimates 919,400 individuals out of work force due to opioids in 2015.¹¹⁷⁰

b. Overdose (“OD”) deaths

- i. A study by Dunn *et al.* found an increased risk of opioid-related overdose death in a step-wise dose response relationship: “Compared with patients receiving 1 to 20 mg/d of opioids (0.2% annual overdose rate), patients receiving 50 to 99 mg/d had a 3.7-fold increase in overdose risk (95% CI, 1.5 to 9.5) and a 0.7% annual overdose rate. Patients receiving 100 mg/d or more had an 8.9-fold increase in overdose risk (CI, 4.0 to 19.7) and a 1.8% annual overdose rate. ... Patients receiving higher doses of prescribed opioids are at increased risk for overdose, which underscores the need for close supervision of these patients.”¹¹⁷¹ The HRs from the Dunn study are represented in the graph at paragraph §C.10.b.iv, below.
- ii. Dunn reported that 4 of the 51 overdose cases (7.8%) “had notes indicating overdoses associated with applying extra fentanyl patches or sucking on a patch.”¹¹⁷² The percentage of overdose cases attributed to fentanyl is much higher than the relatively minor percentage of patients in the study population who used the fentanyl patch (0.6%).¹¹⁷³ This is consistent with fentanyl’s known lethality (50-100 times as potent as heroin), which increases the risk of overdose and death..
- iii. In the Dunn study, the authors noted that the risk analysis was based on a comparison of overdose events among higher dose patients to those who received lower doses, rather than the patients who received none.¹¹⁷⁴ The authors also provided data on the rate of ODs at all levels of exposure, including those with no exposure, and these data further demonstrate the magnitude of increased risk. For the population with no prescribed opioids, the OD rate was 36 per 100,000 person years (PYR), while increasing to 677 per 100,000 PYR at doses of 50-99 mg, and 1791 per 100,000 PYR at doses of 100 mg or greater, representing rate increases of

¹¹⁶⁹ Dale AM, et al. Predictors of long-term opioid use and opioid use disorder among construction works: Analysis of claims data. *Am J Ind Med.* 2021;64(1):48-57, at p. 48

¹¹⁷⁰ Ben Gitis, Isabel Soto, *The Labor Force and Output Consequences of the Opioid Crisis*, American Action Forum (Mar. 27, 2018), <https://www.americanactionforum.org/research/labor-force-output-consequences-opioid-crisis/>.

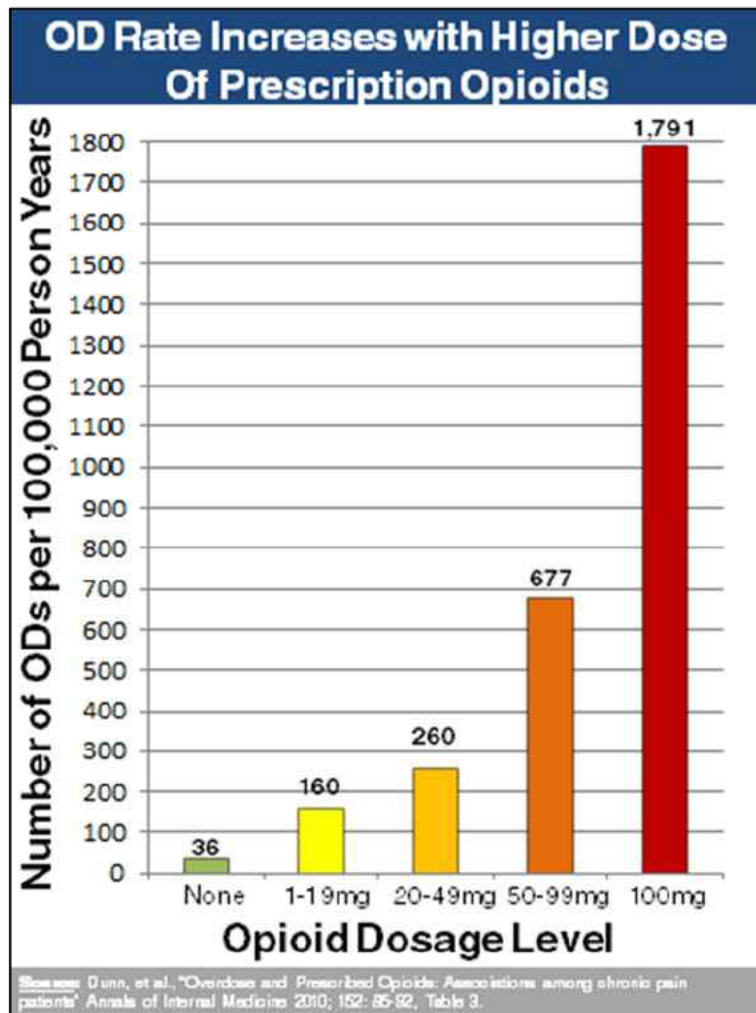
¹¹⁷¹ Dunn KM, Saunders KW, Rutter CM, *et al.* Opioid prescriptions for chronic pain and overdose: A cohort study. *Ann Intern Med.* 2010;152(2):85-92, at p. 85.

¹¹⁷² *Id.* at p. 88.

¹¹⁷³ *Id.* at Table 1, p. 88.

¹¹⁷⁴ *Id.* at p. 90

18.8 and 49.8, respectively, compared to no prescription opioid use.¹¹⁷⁵
 These data are represented in the graph below:



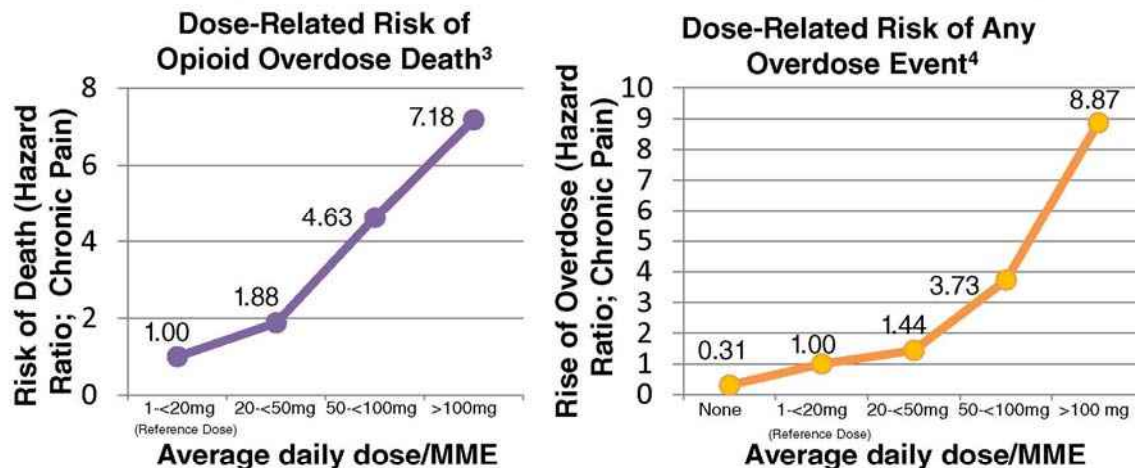
■ Dunn also noted that their study “provides the first estimates that directly link receipt of medically prescribed opioids to overdose risk, and suggests that overdose risk is elevated in patients receiving medically prescribed opioids, particularly in patients receiving higher doses.”¹¹⁷⁶ These are important data, since they directly refute the Industry’s position that only those who misuse the drugs are at risk of OUD and mortality.

¹¹⁷⁵ *Id.* at Table 3, p. 89.

¹¹⁷⁶ *Id.* at p. 90.

“Higher Dosage, Higher Risk”¹

“Higher dosages of opioids are associated with higher risk of overdose and death—even relatively low dosages (20-50 morphine milligram equivalents (MME) per day) increase risk. Higher dosages haven’t been shown to reduce pain over the long term.”²



1. Centers for Disease Control and Prevention, Calculating Total Daily Dose of Opioids For Safer Dosage, https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf.
2. *Id.*
3. Bohnert AS *et al.* Association Between Opioid Prescribing Patterns and Opioid Overdose-Related Deaths. *JAMA*. 2011;305(13):1315-1321. at p. 1319.
4. Dunn KM *et al.* Opioid Prescriptions for Chronic Pain and Overdose. *Ann Intern Med*. 2010;152:85-92, at p. 89.

- As shown in the graph above, studies by Dunn *et al.* and by Bohnert *et al.* both found an increased risk of opioid-related overdose death at each level of increased dose, and particularly at doses greater than 100 MME. In the Dunn study, compared to the reference dose of 1-<20 mg, the adjusted hazard Ratio (HR) for 20-<50 mg was 1.44; for 50-100 mg, the HR was 3.73; and for > 100 mg, the HR was 8.87. In the Bohnert study, compared to the same reference dose of 1 to < 20 MME, the HR for 20 to < 50 mg was 1.88; for 50 to < 100 mg, the hazard ratio was 4.63; and at > 100 mg, the hazard ratio was 7.18. All results were statistically significant. A similar pattern held for each of three diagnostic groups in the Bohnert study (substance use disorders, chronic pain, and cancer): “The adjusted hazard ratios (HRs) associated with a maximum prescribed dose of 100 mg/d or more, compared with the dose category 1 mg/d to less than 20 mg/d, were as follows: among those with substance use disorders, adjusted HR = 4.54 (95% confidence interval [CI], 2.46-8.37; absolute risk difference approximation [ARDA] = 0.14%); among those with chronic pain, adjusted HR = 7.18 (95% CI, 4.85-10.65; ARDA = 0.25%); among those with acute pain, adjusted HR = 6.64 (95% CI, 3.31-13.31; ARDA =

0.23%); and among those with cancer, adjusted HR = 11.99 (95% CI, 4.42-32.56; ARDA = 0.45%).”¹¹⁷⁷ Opioid therapy is generally accepted as appropriate for cancer patients, especially in late stages or severe pain. Nevertheless, with the advent of improved cancer therapies, more patients are living longer with disease or remission, and opioid therapy should be implemented with caution, to minimize risk of addiction.

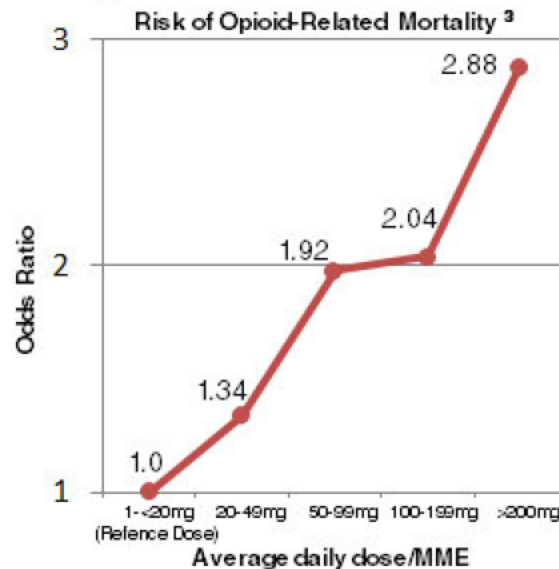
- A population based nested case control study of 607,156 people prescribed opioids found that an average daily dose of 200 mg or more of morphine or equivalent was associated with a nearly 3-fold, statistically significant increased risk of opioid-related mortality relative to low daily doses (< 20 mg of morphine or equivalent), Odds Ratio (OR) 2.88, 95% CI 1.79-4.63.¹¹⁷⁸ This is illustrated in the graph below:

¹¹⁷⁷ Bohnert, et al., “Association Between Prescribing Patterns,” fn. 1083, above, at p. 1315; Olsen, *et al.*, “Pain relief that matters,” fn. 821, above.

¹¹⁷⁸ Gomes *et.al*, “Opioid Dose,” fn. 1129, above, at p. 686. It is noteworthy that Gomes studied “Non-Malignant Pain,” without regard to duration of exposure, requiring only “at least one” opioid prescription in the 120 days prior to death. (p. 687) This may explain the lower relative risk in the Gomes study compared to those in Bohnert (study of pain patients specified those with “chronic pain” conditions) and Dunn (inclusion criteria required 3 or more opioid prescriptions within 90 days prior to the overdose). As Edlund demonstrated, duration of exposure is a key factor in determining the magnitude of increased risk of opioid-related harm.

“Higher Dosage, Higher Risk”¹

“Higher dosages of opioids are associated with higher risk of overdose and death—even relatively low dosages (20-50 morphine milligram equivalents (MME) per day) increase risk. Higher dosages haven’t been shown to reduce pain over the long term.”²



¹Centers for Disease Control and Prevention, Calculating Total Daily Dose of Opioids For Safer Dosage, https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf.

²Id.

³Gomes T, et al. Opioid Dose and Drug-Related Mortality in Patients with Nonmalignant Pain. *Arch Intern Med.* 2011;171(7): 686-691, at p. 690

- vii. A study of U.S. adolescents and young adults found that “approximately 1 in 10,000 adolescents and young adults overdosed while they had an active opioid prescription.”¹¹⁷⁹ Further, in adjusted analyses “each increase in daily opioid dosage category was associated with an 18% higher odds of overdose.”¹¹⁸⁰
- viii. A recent retrospective cohort study of over 2 million individuals newly dispensed an opioid for pain between July 2013 and March 2016 found that 525 of 1121 overdoses (46.8%) occurred while patients were actively being treated with prescription opioids,¹¹⁸¹ which further supports that patients using opioids for medical reasons are at risk of overdose. The study further found that 289 of 1121 (25.5%) of the overdoses occurred within the first 28 days following initiation of the prescription and that the odds of long-term use (> 1 year) were 8-fold higher with > 30 days initial

¹¹⁷⁹ Chua K-P, Brummett CM, Conti RM, Bohnert A. Association of opioid prescribing patterns with prescription opioid overdose in adolescents and young adults. *JAMA Pediatr.* 2020;174(2):141-148, at p. 146.

¹¹⁸⁰ Id.

¹¹⁸¹ Gomes T, et al. Initial opioid prescription patterns and the risk of ongoing use and adverse outcomes. *Pharmacoepidemiol Drug Saf.* 2020;1-11, at p. 6.

prescription compared to 2 days or less initial prescription length, and even prescriptions of 3-4 days conferred a 19% increased risk of OD compared to 2 days or less.¹¹⁸² While the study cannot rule out that patients may have been using non-prescribed opioids along with the prescribed opioids, the fact that nearly half were in active treatment, and that the risk increased with the prescribed dose, strongly implicate the prescription opioids as at least contributing factors to the overdoses.

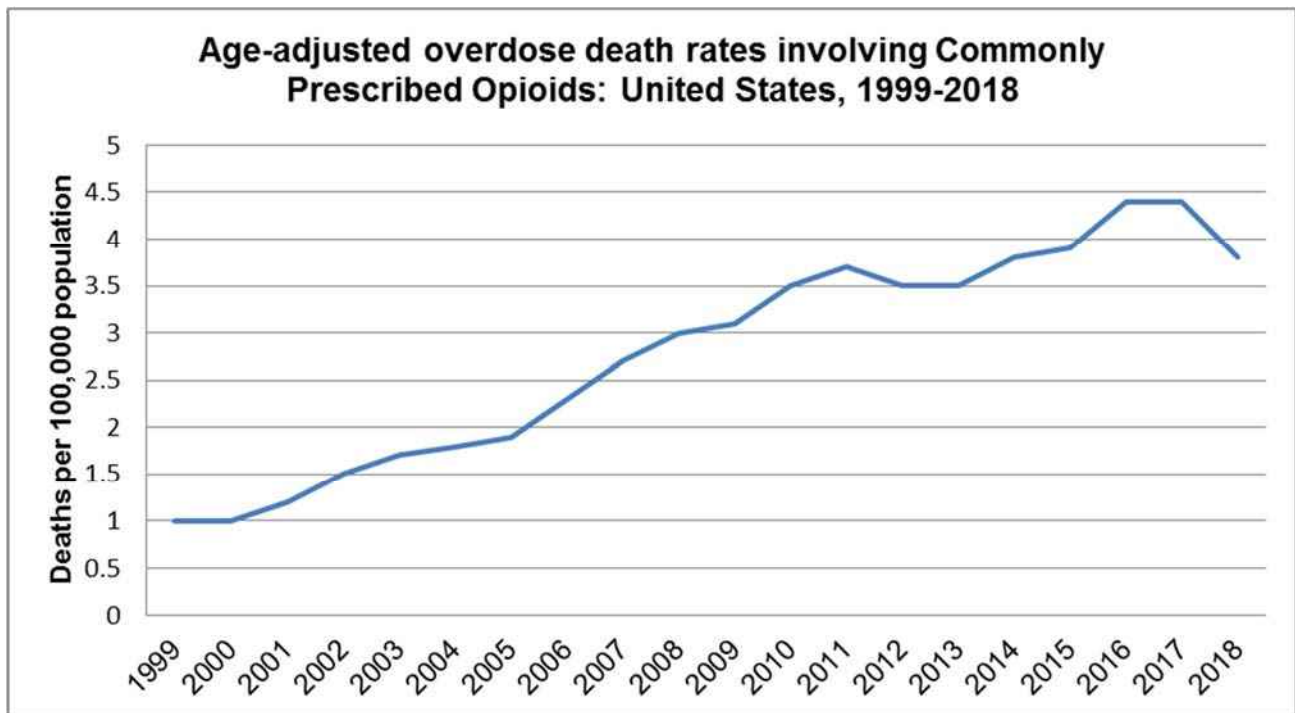
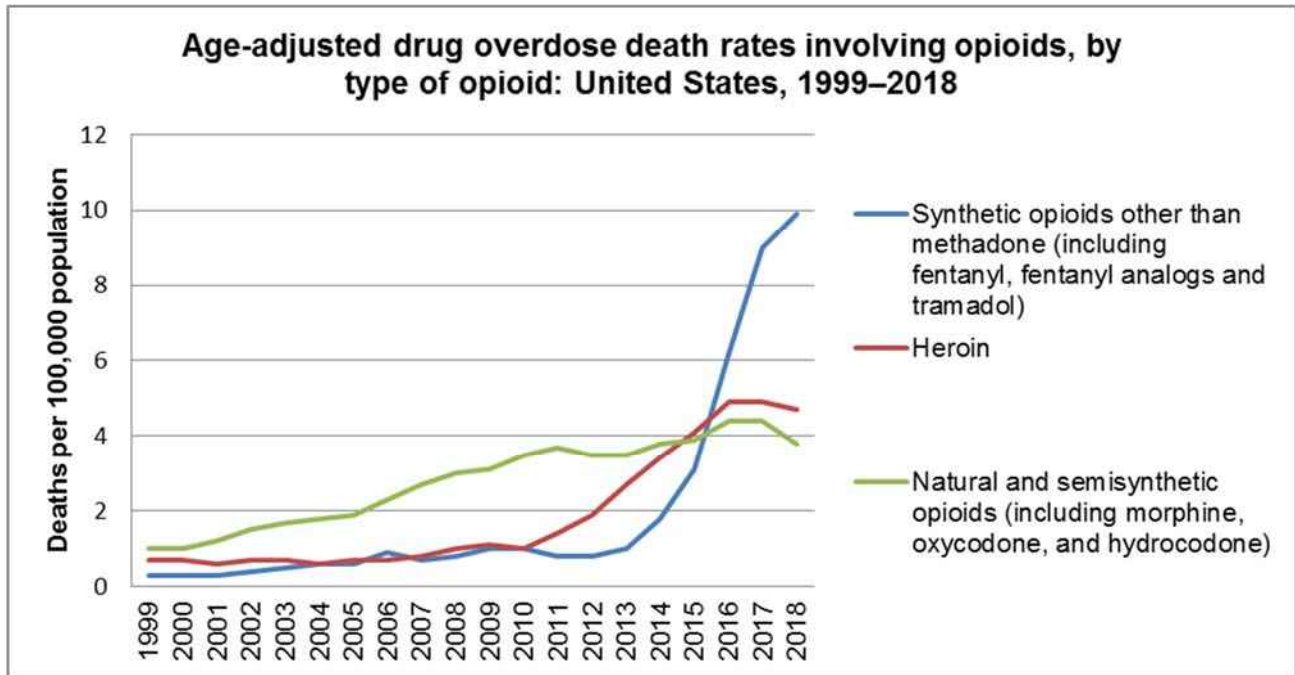
- ix. A 2019 cohort study from the United Kingdom examined 98,140 new long-term (three or more opioid prescriptions within 90 days) opioid users for 3.4 years. The authors found that “[l]ong-term opioid use is associated with serious adverse events such as major trauma, addiction and overdose. The risk increases with higher opioid doses.”¹¹⁸³
- x. The evidence of increased dose as the cause of higher mortality is supported by evidence of the converse, that is, lower mortality following decreased dose. Recent experience in Oregon demonstrated a significant decrease in overdose deaths after policies were implemented to prioritize non-opioid pain management and to lower the doses when opioid therapy was prescribed.¹¹⁸⁴
- xi. We are now in the second and third waves of this epidemic, with a spike in deaths from illicit opioids, particularly heroin (second wave) and illicit fentanyl (third wave). The prescription opioid epidemic led to transition to heroin/fentanyl, and the cumulative death toll remains higher for prescription opioids, despite recent spikes in fentanyl-related mortality.
- xii. Based on CDC data, between 1999 and 2018, 245,218 people died from opioid pain relievers (excluding non-methadone synthetics, predominantly fentanyl). In the same time period, 115,568 died from heroin, and 124,486 people died from non-methadone synthetics (predominantly fentanyl), for a total of 240,054 deaths due to heroin and illicit fentanyl. Although these numbers are staggering, the cumulative death toll from opioid pain relievers through 2018 (245,218) was more than that of heroin and illicit

¹¹⁸² *Id.*, at pp. 6, 8.

¹¹⁸³ Bedson J, Chen Y, Ashworth J, Hayward RA, Dunn KM, Jordan KP. Risk of adverse events in patients prescribed long-term opioids: A cohort study in the UK Clinical Practice Research Datalink. *Eur J Pain*. 2019; 23:908-922, at p. 908.

¹¹⁸⁴ Hedberg K, et al. Integrating public health and health care strategies to address the opioid epidemic: the Oregon Health Authority’s opioid initiative. *Journal of Public Health Management & Practice*. 2019;25(2):214-220, at pp. 214-215.

fentanyl combined (240,054).¹¹⁸⁵ The graphs below show the changes in opioid death rates over time.¹¹⁸⁶



¹¹⁸⁵ Centers for Disease Control and Prevention, *Data Brief 356. Drug Overdose Deaths in the United States, 1999–2018*, https://www.cdc.gov/nchs/data/databriefs/db356_tables-508.pdf, at Data Table for Figure 3,

¹¹⁸⁶ Graphs generated from data provided by *Id.*

- xiii. Prescription opioid related deaths, excluding fentanyl and methadone, continued to rise through 2017, with 2018 registering the first substantial annual decline in prescription opioid related deaths since 1999 (14,495 deaths in 2017; 12,550 in 2018).¹¹⁸⁷ A 2019 report released by the CDC shows that drug overdose deaths in women aged 30-64 years due to prescription opioids have been steadily rising between 1999 and 2017. “The crude rate for deaths involving prescription opioids increased from 1999 to 2017 for every age group, with the largest increases (>1,000%) among women aged 55–64 years.”¹¹⁸⁸
- xiv. In 2019, 36,659 drug overdose deaths involved non-methadone synthetic opioids (primarily illicitly manufactured fentanyl), 14,019 deaths involved heroin and 14,626 deaths involved opioid pain relievers.¹¹⁸⁹
- Provisional data for the period May 2019-May 2020 show “the highest number of overdose deaths ever recorded in a 12-month period” with over 81,000 drug overdose deaths.¹¹⁹⁰ Synthetic opioids (illicitly manufactured fentanyl) “appear to be the primary driver of the increases in overdose deaths” with 10 western states reporting an over 98% increase in fentanyl-involved overdose deaths.¹¹⁹¹ According to the CDC, “While overdose deaths were already increasing in the months preceding the 2019 novel coronavirus disease (COVID-19) pandemic, the latest numbers suggest an acceleration of overdose deaths during the pandemic.”¹¹⁹²
- xvi. In short, as shown in the graphs above, while there has been an obvious recent spike in deaths related to heroin and illicit fentanyl, the number of deaths caused by non-fentanyl prescription opioids has continued to be unacceptably high, and approximately four times greater than in 1999.

c. Nonfatal overdose

- While fatal cases justifiably capture our attention, it must also be recognized that the cost of a nonfatal overdose is far greater in terms of medical and community resources, both in terms of medical costs to treat the overdose episode itself, and to provide long-term care for an OUD that may have given rise to the overdose event.

¹¹⁸⁷ *Id.*

¹¹⁸⁸ VanHouten JP, Rudd RA, Ballesteros MF, Mack KA. Drug Overdose Deaths Among Women Aged 30–64 Years — United States, 1999–2017. *MMWR Morb Mortal Wkly Rep.* 2019;68(1):1-5, at p. 2.

¹¹⁸⁹ Hedegaard H. et al. *Drug overdose deaths in the United States, 1999-2019. NCHS Data Brief No. 394.* <https://www.cdc.gov/nchs/products/databriefs/db394.htm>, at Data Table for Figure 3.

¹¹⁹⁰ Centers for Disease Control and Prevention, Overdose deaths accelerating during Covid-19, (December 17, 2020), <https://www.cdc.gov/media/releases/2020/p1218-overdose-deaths-covid-19.html>, at p. 1.

¹¹⁹¹ *Id.*

¹¹⁹² *Id.*

- ii. According to the CDC, among approximately 45 million emergency department visits reported by the 16 Enhanced State Opioid Overdose Surveillance (ESOOS) states from July 2016 through September 2017, “a total of 119,198 (26.7 per 10,000 visits) were suspected opioid overdoses.”¹¹⁹³ Between 2009 and 2014, Ohio recorded a 106.4% increase in rates of opioid-related emergency department visits, the highest of any state.¹¹⁹⁴
- iii. Unlike the available fatal overdose data, which are categorized according to non-fentanyl prescription opioids, heroin, etc., the CDC/ESOOS on emergency department visits are not broken out into categories. Although the cumulative total of prescription opioid mortality since 1999 exceeds mortality for fentanyl plus heroin, the mortality rate for the latter category has recently begun to exceed the former; it is likely that the nonfatal overdose hospital admissions have occurred in a similar ratio of prescription opioids to illicit heroin and fentanyl.
- iv. Tens of thousands of Americans experience non-fatal overdose, both in medical settings, like the emergency department, and in the field, creating a significant burden on the health care system and on first responders, not to mention the victims of near overdose themselves. In the paper by Dunn *et al.*, previously discussed, the authors found “[m]ore than 7 nonfatal overdose events occurred for each fatal overdose” in the study cohort.¹¹⁹⁵ “The overall overdose rate in the sample was 148 per 100,000 person-years, indicating that fatal overdose represents only the tip of the iceberg (88% of identified overdose events were nonfatal). Most of the nonfatal overdoses were clinically serious.”¹¹⁹⁶ These data mean that on a nationwide basis, the over 14,000 fatal prescription opioid overdoses in 2017¹¹⁹⁷ would translate to over 100,000 nonfatal overdoses during that same year.

d. Suicide

- i. The 2019 cohort study from the United Kingdom which examined 98,140 new long-term (three or more opioid prescriptions within 90 days) opioid users for 3.4 years, and found that long-term use was associated with serious adverse events, also found that the risk of suicide by intentional

¹¹⁹³ Vivolo-Kantor AM, Seth P, Gladden RM, *et al.* Vital Signs: Trends in Emergency Department Visits for Suspected Opioid Overdoses — United States, July 2016–September 2017. *MMWR Morb Mortal Wkly Rep.* 2018;67:279–285, at p. 281.

¹¹⁹⁴ Weiss AJ, *et al.* Opioid-Related Inpatient Stays and Emergency Department Visits by State, 2009-2014. HCUP Statistical Brief #219. December 2016. Agency for Healthcare Research and Quality, Rockville, MD. <http://www.hcup-us.ahrq.gov/reports/statbriefs/sb219-Opioid-Hospital-Stays-ED-Visits-by-State.pdf>

¹¹⁹⁵ Dunn, *et al.*, “Opioid Prescriptions,” fn. 1171, above, at p. 89.

¹¹⁹⁶ *Id.*, p. 91.

¹¹⁹⁷ CDC, Data Brief 356, fn. 1185, above, at p. 4.

overdose increases with higher opioid doses.”¹¹⁹⁸ The authors also report that intentional opioid overdose was nearly 4x more likely in patients prescribed long-term opioids at the highest doses (>50mg).¹¹⁹⁹

- ii. Writing in the journal *Pain*, Ilgen *et al.* found that the higher the dose of opioids, the greater the suicide risk, an association which was not present in patients with chronic pain on acetaminophen, a non-opioid pain pill. The authors write, “Increased dose of opioids was found to be a marker of increased suicide risk, even when relevant demographic and clinical factors were statistically controlled There was no significant association between acetaminophen dose and regimen and suicide risk, suggesting that the observed effects may be specific to opioids.”¹²⁰⁰
- iii. In a *New England Journal of Medicine* article on opioids and suicide risk, Bohnert *et al.* note that “A reduction in the quantity of prescribed opioids may function as a ‘means restriction’ by reducing patients’ access to a lethal means of causing an intentional or unintentional opioid overdose. To this end, clinicians should ask about their patients’ access to opioids, including past prescriptions and medications prescribed to others in the same home. Taper protocols that involve small decreases in dosage over time are successful for reducing dosages and may actually reduce pain intensity. However, whether tapering changes the risk of either suicide or overdose is unknown.”¹²⁰¹
- iv. As above, intentional opioid overdose, *i.e.* suicide, was nearly 4x more likely in patients prescribed long-term opioids at the highest doses (>50mg).¹²⁰²
- v. A Veterans Health Administration study examining the likelihood of death from overdose or suicide in veterans prescribed opioid analgesics in the early implementation period of VHA’s opioid safety initiative (2014-2016) found that “All patients exposed to opioids had an increased risk of death from overdose or suicide after starting or stopping treatment with opioids. Although patients treated with opioids for long periods (eg, >400 days in our evaluation) had the highest hazard ratios after stopping treatment, even those treated for up to 30 days had a rise in the risk of death after treatment was stopped (hazard ratio of 1.4 for death from overdose after stopping opioid treatment and 1.7 for death from overdose

¹¹⁹⁸ Bedson, “Risk of adverse events”, fn. 1183, above, at p. 908.

¹¹⁹⁹ *Id.* at p. 913.

¹²⁰⁰ Ilgen MA, Bohnert AS, *et al.* Opioid Dose and Risk of Suicide. *Pain*. 2016 May; 157(5): 1079–1084. doi:10.1097/j.pain.0000000000000484, at p. 5.

¹²⁰¹ Bohnert ASB, Ilgen MA. Understanding Links among Opioid Use, Overdose, and Suicide. *N Engl J Med*. 2019. doi:10.1056/nejmra1802148, at p. 76.

¹²⁰² Bedson *et al.* “Risk of Adverse Events”, fn. 1183, above, at p. 913.

or suicide). Those treated with opioids for 31-90 days had a hazard ratio of 2.4 for death from overdose after stopping opioid treatment (2.8 for death from overdose or suicide).”¹²⁰³ In other words, opioids increase the risk of overdose death in the initiation phase, the maintenance phase, and the discontinuation phase, highlighting the lethality of these drugs at all stages of treatment. Further, risks increase with increasing dose and duration.¹²⁰⁴

- e. Opioids are associated with more adverse medical outcomes and increased mortality and morbidity than non-opioid analgesics (NSAIDs),¹²⁰⁵ contrary to the claim that morbidity and mortality of non-opioid medications (NSAIDs) for pain are comparable.¹²⁰⁶
- f. The opioid epidemic is also partly responsible for the spread of Hepatitis C, HIV and other infectious diseases across the country in recent years, as people who become addicted to prescription opioids, transition to injection drug use and share needles with others who are infected. For example, the outbreak of Hepatitis C and HIV in Scott County, Indiana in 2015, “resulted from inappropriate prescribing of opioid medications.”¹²⁰⁷
- g. Misuse and addiction
 - i. As discussed in this report, above, misuse of prescription opioids and addiction are significant problems throughout the United States; prescription opioids have been a major stepping stone for illicit opioid use and resulting harms; and over-prescribing contributes to population risk of opioid related harms.
 - ii. 11 million people misused prescription opioids in 2016, compared to the approximately 1 million people using heroin. In 2011, according to a CDC report, 11 million people reported nonmedical use of opioid analgesics. “Moreover, chronic nonmedical use of opioid analgesics (*i.e.* nonmedical use on 200 days or more in the past year) increased roughly 75% between 2002-2003 and 2009-2010. This increase means that on average in 2009-

¹²⁰³ Oliva EM, *et al.* Associations between stopping prescriptions for opioids, length of opioid treatment, and overdose or suicide deaths in US veterans: Observational evaluation. *BMJ*. 2020;368:m283:1-10, at p. 6. The study “did not take into consideration the reasons or clinical intentions for stopping, or the speed of its execution.”

¹²⁰⁴ *Id.*, at p. 6.

¹²⁰⁵ Solomon DH, Rassen JA, Glynn RJ, Lee J, Levin R, Schneeweiss S. The comparative safety of analgesics in older adults with arthritis. *Arch Intern Med*. 2010;170(22):1968-1976. doi:10.1001/archinternmed.2010.391, at p. 1968.

¹²⁰⁶ Tayeb BO, Barreiro AE, Bradshaw YS, Chui KKH, Carr DB. Durations of opioid, non-opioid drug, and behavioral clinical trials for chronic pain: Adequate or inadequate? *Pain Med (United States)*. 2016. doi:10.1093/PM/PNW245, at p. 2043.

¹²⁰⁷ Strathdee SA, Beyrer C. Threading the Needle — How to Stop the HIV Outbreak in Rural Indiana. *N Engl J Med*. 2015. doi:10.1056/NEJMp1507252, at p. 398.

2010 there were nearly 1 million people in the U.S. with chronic nonmedical use of opioid analgesics.”¹²⁰⁸

- Nearly 2 million (0.8%) of people in the United States are addicted to opioids based on estimates from the 2015 National Survey on Drug Use and Health (NSDUH).¹²⁰⁹
- iv. Even among cancer patients, the rates of opioid misuse and addiction is very high, with a recent study finding that 19% of cancer patients taking opioids for cancer pain develop nonmedical opioid use (ie, misuse) within a median duration of 8 weeks after initial supportive care clinic consultation.¹²¹⁰

13. There is no doubt that a cause-and-effect relationship exists between the oversupply of prescription opioids and the opioid epidemic.

- i. Defense experts in this litigation have repeatedly and mistakenly claimed that the prescription opioid oversupply and the opioid epidemic are associated but not causally linked.¹²¹¹ Defendants’ denial of causation parallels the history of smoking and cancer. For much of the 20th century, scientific literature had reported an “association” between exposure to cigarettes and the occurrence of lung cancer, that is, lung cancer was found to have occurred more frequently among smokers. However, cigarette manufacturers denied that their products had “caused” the increased number of lung cancer cases and relied upon publications that attributed the association to other factors.

¹²⁰⁸ United States Dep’t of Health and Human Servs. *Addressing Prescription Drug Abuse in the United States*. 1-36, at pp., 9-10, https://www.cdc.gov/drugoverdose/pdf/hhs_prescription_drug_abuse_report_09.2013.pdf.

¹²⁰⁹ Han B, Compton WM, Blanco C, Crane E, Lee J, Jones CM. Prescription Opioid Use, Misuse, and Use Disorders in U.S. Adults: 2015 National Survey on Drug Use and Health. *Annals of Internal Medicine*. 2017;167(5):293-301. Epub 2017/08/02. doi: 10.7326/m17-0865. PubMed PMID: 28761945, at 293.

¹²¹⁰ Yennurajalingam S, *et al.* Frequency of and factors associated with nonmedical opioid use behavior among patients with cancer receiving opioids for cancer pain. *JAMA Oncol*. 2021;1-8. Doi:10.1001/jamaoncol.2020.6789, at 1.

¹²¹¹ See, e.g., Expert Report of Rob Lyerla. *In re: Nat’l Prescription Opiate Litig.*, No. 1:17-MD-2804 (May 10, 2019) (“Plaintiffs’ experts purport to demonstrate a causal relationship between opioid use and opioid misuse and mortality. However, the data they use are insufficient to support their conclusions.”), Expert Report of Stephanie W. Colston, *City of Huntington, West Virginia et al. v. AmerisourceBergen Drug Corporation et al.*, Case No. 3:17-01362 (August 27, 2020) (“A substantial body of empirical evidence documents that prescription opioids are not the causal culprit of the opioids abuse crisis. These studies document that the root causes of the opioid abuse crisis are considerably broader than supply alone and, in addition, the studies demonstrate that supply-only responses to the opioids abuse crisis have had deleterious public health and safety consequences.”), Expert Report of Peggy Compton, *City of Huntington, West Virginia et al. v. AmerisourceBergen Drug Corporation et al.*, Case No. 3:17-01362 (August 27, 2020) (“persons with opioid use disorder will seeks opioids from many sources, including a physician, however this should not be interpreted to mean that the prescribed opioid is causally related to the development of addiction.”), and Expert Report of Kevin M. Murphy, *City of Huntington, West Virginia et al. v. AmerisourceBergen Drug Corporation et al.*, Case No. 3:17-01362 (August 27, 2020) (“An association between opioid supply and opioid mortality (or other opioid-related harms) does not establish a causal link.”).

- ii. In 1956, the noted British epidemiologists, Sir Richard Doll and Sir Austin Bradford Hill published an influential study of smoking and lung cancer among physicians in Britain. This article recounted and rejected alternative explanations for the increase in lung cancer, e.g., “that smoking does not produce cancer in a person in whom cancer would not otherwise have occurred at all, but merely determines the primary site of a growth that is destined to appear in some part of the body,”¹²¹² and that “atmospheric pollution” might explain the increased risk.¹²¹³
- Doll and Hill observed a higher mortality in smokers than in non-smokers, a higher mortality in heavy smokers than in light smokers, and a higher mortality in those who continued to smoke than in those who gave it up.¹²¹⁴ In 1964, their study became part of the data set that resulted in the 1964 Report of the United States Surgeon General that “cigarette smoking is causally related to lung cancer in men; the magnitude of the effect of cigarette smoking far outweighs other factors. The data for women, though less extensive, point in the same direction.”¹²¹⁵
- iv. In 1965, one of the authors of that landmark smoking study, Sir Austin Bradford Hill, published an essay that has become the framework for answering the question of when a statistical finding of association meets threshold criteria for causation: “What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?”¹²¹⁶ The “Bradford Hill factors,” as they have become known, are generally accepted in the scientific literature, as the leading methodology to determine whether there is a causal relationship between exposure to a risk factor and the occurrence of disease.¹²¹⁷
- v. The factors cited by Bradford Hill to determine whether an association is causal are as follows: (1) Strength of the association, (2) Consistency, (3) Specificity (4) Temporality, (5) Dose-response relationship, sometimes called “biological gradient,” (6) Plausibility (7) Coherence, (8)

¹²¹² Doll and Hill. Lung Cancer and Other Causes of Death in Relation to Smoking: A Second Report on the Mortality of British Doctors. *British Medical Journal*, 1956, 1071-1081, at 1077.

¹²¹³ *Id.*, at 1078.

¹²¹⁴ *Id.*, at 1081.

¹²¹⁵ Report of the Advisory Committee to the Surgeon General, *Smoking and Health*. Public Health Service Publication No.1103, January 1964. <https://profiles.nlm.nih.gov/spotlight/nn/catalog.nlm.nlmuid-101584932X204-doc>, at 31.

¹²¹⁶ Hill AB, The Environment and Disease: Association or Causation?, fn. 97, above.

¹²¹⁷ I am aware that Judge Polster cited the Bradford-Hill factors, and the Federal Judicial Center’s *Reference Manual on Scientific Evidence* that lists those factors, in his Order denying the MDL Defendants’ motion to exclude my opinions. See Order Denying Defendants’ Motion to Exclude Expert Testimony of Katherine Keyes, Anna Lembke and Jonathan Gruber re the “Gateway Hypothesis” of Causation, *In re: Nat’l Prescription Opiate Litig.*, No. 1:17-MD-2804, 2019 WL 4043943 (N.D. Ohio Aug. 26, 2019), at 11-12.

Experiment,¹²¹⁸ and (9) Analogy. These factors are a guide, not a checklist: “There is no formula or algorithm that can be used to assess whether a causal inference is appropriate based on these guidelines. One or more factors may be absent even when a true causal relationship exists. Similarly, the existence of some factors does not ensure that a causal relationship exists. Drawing causal inferences after finding an association and considering these factors requires judgment and searching analysis, based on biology, of why a factor or factors may be absent despite a causal relationship, and vice versa. Although the drawing of causal inferences is informed by scientific expertise, it is not a determination that is made by using an objective or algorithmic methodology. These guidelines reflect criteria proposed by the U.S. Surgeon General in 1964 in assessing the relationship between smoking and lung cancer and expanded upon by Sir Austin Bradford Hill in 1965 and are often referred to as the Hill criteria or Hill factors.”¹²¹⁹

- vi. As summarized below, the sources cited in this Report provide more than sufficient evidence that there is a causal relationship between prescription opioids, their oversupply, and the various harms described, based on this generally accepted methodology. There are numerous parallels to the relationship between smoking and lung cancer, including strength of association, dose-response relationship, temporality, and consistency across multiple studies. An additional parallel is that widespread increased access to and promotion of cigarettes gave rise to more young people starting smoking and fewer users quitting; as well as contributed to greater consumption among users across the United States.¹²²⁰
- vii. In evaluating the evidence, the factors of strength of association, consistency, temporality, dose-response, biological plausibility, and experiment/cessation of exposure are most important.
- viii. Bradford Hill’s article states as follows: “(1) *Strength*. First upon my list I would put the strength of the association.”¹²²¹ Regarding this factor, the

¹²¹⁸ The factor of “Experiment” is referred to as “Cessation of Exposure” in the set of “Hill factors” provided by the Federal Judicial Center, *Reference Manual on Scientific Evidence* (3rd edition, 2011), which states: “If an agent is a cause of a disease, then one would expect that cessation of exposure to that agent ordinarily would reduce the risk of the disease. This has been the case, for example, with *cigarette smoking and lung cancer*. . . . [W]hen such data are available and eliminating exposure reduces the incidence of disease, this factor strongly supports a causal relationship.” (*Id.*, at 605; emphasis added). This formulation closely matches Bradford Hill’s description of the “Experiment” factor: “Occasionally it is possible to appeal to experimental, or semi-experimental, evidence. For example, because of an observed association *some preventive action is taken. Does it in fact prevent?* The dust in the workshop is reduced, lubricating oils are changed, *persons stop smoking cigarettes. Is the frequency of the associated events affected? Here the strongest support for the causation hypothesis may be revealed.*” Hill AB, The Environment and Disease, fn. 97, above, at 298-299 (emphasis added).

¹²¹⁹ Federal Judicial Center, *Reference Manual on Scientific Evidence*, 3rd edition, 2011, at 599-600.

¹²²⁰ U.S. Surgeon General, *Preventing Tobacco Use Among Youth and Young Adults*. 2012, at Chapter 5, p. 487.

¹²²¹ Hill AB, The Environment and Disease, fn. 97, above, at 295. (emphasis in original).

Reference Manual on Scientific Evidence states: “The relative risk is one of the cornerstones for causal inferences. Relative risk measures the strength of the association. The higher the relative risk, the greater the likelihood that the relationship is causal. For cigarette smoking, for example, the estimated relative risk for lung cancer is very high, about 10. That is, the risk of lung cancer in smokers is approximately 10 times the risk in nonsmokers. A relative risk of 10, as seen with smoking and lung cancer, is so high that it is extremely difficult to imagine any bias or confounding factor that might account for it. The higher the relative risk, the stronger the association and the lower the chance that the effect is spurious.”¹²²²

- ix. A standard textbook in epidemiology, written by a Professor at the Harvard School of Public Health, describes ratios of between 3.0 and 10.0 as “strong,” and a ratio of over 10.0 as “infinite,” meaning that it is extremely unlikely to be explained by any confounding or bias.¹²²³
- There are two complementary and mutually reinforcing perspectives to view the strength of association between prescription opioids and adverse outcomes such as addiction and mortality. First is the association found in specific exposed populations; second is the association found on a national level, as a result of prescription opioid promotion, sale, and distribution. These are addressed below.
- Strength of association in specific exposed populations: The evidence in this case shows “strong” and even “infinite” ratios of death and disease among specific populations exposed to prescription opioids, compared to unexposed subjects. The peer-reviewed Edlund study discussed at Section §C.4, analyzed claims and prescription information from two large healthcare databases. The study reported exceptionally high hazard ratios (HRs) of 14.92, 28.69, and 122.45 for diagnosis of opioid addiction among subjects with low, moderate, and high-dose chronic (> 90 days) exposure to prescription opioids, respectively, compared to subjects with no exposure to prescription opioids. All of these ratios exceed the relative risk of 10 for smoking and lung cancer, and also exceed a threshold for “infinite” association. Indeed, for patients on prescription opioids equivalent to 120 mg of morphine daily for three months or more, the risk of becoming addicted to opioids as a result of that prescription is more than ten times the risk of developing lung cancer as a result of smoking cigarettes. The data therefore provide exceptionally strong support for causality of opioid addiction by chronic exposure to prescription opioids.

¹²²² Federal Judicial Center, *Reference Manual on Scientific Evidence*, 3rd edition, 2011, at 602. See also, 1964 Surgeon General’s report at Table 2, p. 29, citing 10.8x higher rate of lung cancer among smokers compared to non-smokers.

¹²²³ See, e.g., Monson, Richard. *Occupational Epidemiology*. CRC Press. (2nd edition, 1990), at 88.

- xiii. Strong associations are also demonstrated between prescription opioid exposure and fatal/nonfatal overdose, among specific populations. The peer-reviewed study by Dunn, discussed in Section §C.12.b of this Report, reported HR of 8.87 for opioid overdose, including fatal and non-fatal, among members of a Washington State healthcare organization who were exposed to prescription opioids > 100 MME per day, compared to subjects without prescription opioid exposure; the Bohnert study, also discussed at Section §C.12.b, showed a similar HR of 7.19 for fatal overdose among Veterans Health Administration patients exposed to > 100 MME per day, compared to subjects with < 20 MME per day. Both of these HRs are toward the upper end of the “strong” category of association. Defense experts fail to address the importance of these strong associations that support causation.
- xiii. Analogous increased rates of prescription opioid overdose have been demonstrated in state and national data sets since the oversupply began in the late 1990s. “From 1999 to 2007 in Ohio, there were increases of 304 percent and 325 percent, respectively in the unintentional drug poisoning death rate and total grams of prescription opioids distributed per 100,000 population.”¹²²⁴ Based on these data, the Ohio Department of Health concluded, “There is a *strong relationship* between increases in sales of prescription opioids and fatal unintentional drug poisoning rates.”¹²²⁵ This “strong” relationship was enabled by widespread distribution, resulting in over a three-fold increase in per capita prescriptions. Similar increased prescription opioid sales, distribution, mortality and hospitalization occurred nationally, as shown in Section §C.3.b of this Report. As noted by CDC authors, “Increased use of OPR [Opioid pain Relievers] has contributed to the overall increases in rates of overdose death and nonmedical use, and variation among states in OPR sales probably contributes to state variation in these outcomes.”¹²²⁶
- xiv. There is essentially uniform agreement in the published literature that promotion and widespread distribution of prescription opioids resulted in

¹²²⁴ Ohio Department of Health, Violence and Injury Prevention Program. “Epidemic of Prescription Drug Overdose in Ohio, 1999-2009,” July 18, 2018, at 2. https://odh.ohio.gov/wps/wcm/connect/gov/5a0bbf8a-8d88-49e5-bd6c-56ca28c2104c/Epidemic_of_Prescription_Drug_Overdose_Ohio_Report.pdf?MOD=AJPERES&CONVERT_TO=url&CACHEID=ROOTWORKSPACE.Z18_M1HGGIK0N0JO00QO9DDDDM3000-5a0bbf8a-8d88-49e5-bd6c-56ca28c2104c-miUpbk3

¹²²⁵ *Id.*, (emphasis added).

¹²²⁶ Paulozzi, et al., Vital Signs: Overdoses of Prescription Opioid Pain Relievers --- United States, 1999—2008. *MMWR*, November 4, 2011 / 60(43);1487-1492. See also, Walley, Alexander Y., et al. “The contribution of prescribed and illicit opioids to fatal overdoses in Massachusetts, 2013-2015.” *Public Health Reports* 134.6 (2019): 667-674., <https://doi.org/10.1177/0033354919878429>, at 667. “In the United States in the 1990s and early 2000s, annual increases in opioid-related overdose deaths and entries into treatment for opioid addiction paralleled increases in prescriptions of opioid medications for pain. *This correlation appears to have been causal*, as the expansion of opioid prescribing for pain led to more persons overdosing on opioids and more persons seeking treatment for opioid use disorder.” (emphasis added).

the oversupply that gave rise to the epidemic of addiction and mortality. As noted previously, the NASEM and ASPPH reports, both highly reputable and respected sources, identified aggressive marketing, including misleading promotion by some, as well as distribution throughout the country, as key factors contributing to the epidemic.¹²²⁷

- xv. (2) *Consistency* refers to whether similar findings have been “repeatedly observed by different persons, in different places, circumstances and times.”¹²²⁸ As with the factor of “Strength of Association,” *Consistency* is also apparent in specific study populations as well as state and national data sets. Numerous references cited in this Report provide consistency of the observed relationship between prescription opioids and the adverse outcomes of opioid addiction and overdose in particular populations.
- Consistent with the Edlund study, Papadomanolakis-Pakis was an incidence study that reported risk of opioid addiction among Ontario, Canada residents whose records were part of a healthcare database; HRs in that study increased with duration of the initial opioid prescription.¹²²⁹ As discussed in Section §C.8.b of this Report, the Vowles systematic review found elevated risks of addiction and misuse in 38 studies of chronic pain patients exposed to prescription opioids, and the Boscarino study reported similarly elevated risks.
- xvii. The relationship between increased prescription *opioid sales* and increased drug overdose mortality has also been demonstrated repeatedly, and consistently. As noted above in the discussion of Strength of Association, the Ohio Department of Health reported, based on data from 1999-2009, “There is a strong relationship between increases in sales of prescription opioids and fatal unintentional drug poisoning rates.”¹²³⁰ The CDC data showed a similar relationship at the national level.¹²³¹ These similar findings support the Hill factor of Consistency, as well as Strength of Association.
- xviii. (3) *Temporality*: “A temporal, or chronological, relationship must exist for causation to exist. If an exposure causes disease, the exposure must occur before the disease develops. If the exposure occurs after the disease

¹²²⁷ See Section §C.2.i of this Report, above.

¹²²⁸ Hill AB, The Environment and Disease, “Environment and Disease” fn. 97, above, at 296. (emphasis in original)

¹²²⁹ Papadomanolakis-Pakis, N, *et al.* Prescription opioid characteristics at initiation for non-cancer pain and risk of treated opioid use disorder: A population-based study. *Drug and Alcohol Dependence*. 2021;221:1-9.

¹²³⁰ Ohio Department of Health, Violence and Injury Prevention Program. “Epidemic of Prescription Drug Overdose in Ohio, 1999-2009,” July 18, 2018, at p.2. https://odh.ohio.gov/wps/wcm/connect/gov/5a0bbf8a-8d88-49e5-bd6c-56ca28c2104c/Epidemic_of_Prescription_Drug_Overdose_Ohio_Report.pdf?MOD=AJPERES&CONVERT_TO=url&CACHEID=ROOTWORKSPACE.Z18_M1HGGIK0N0JO00QO9DDDDM3000-5a0bbf8a-8d88-49e5-bd6c-56ca28c2104c-miUpbk3

¹²³¹ See data and graph at Section §C.3.b above.

develops, it cannot have caused the disease.” *Temporality* is established in both specific study populations and national data sets.

- xix. The incidence studies (Edlund, Papadomanolakis-Pakis) cited above demonstrate that diagnoses of opioid addiction followed exposure to prescription opioids, since the study designs excluded subjects with opioid addiction prior to the beginning of the study period. Temporality was also shown in a study reporting that “exposure to opioids through a dental clinician in a population of opioid naïve patients was associated with higher use of opioids at 90 to 365 days later and subsequent diagnoses associated with opioid abuse or overdose compared with controls. ... [T]he higher probability of abuse diagnoses in the exposed cohort suggests that many of the repeated opioid prescriptions in this cohort were related to substance abuse.”¹²³² The authors reported subsequent opioid prescriptions at 90 to 365 days among 6.9% of the dental patients who received opioids, compared to only 0.1% of those treated with non-opioids.¹²³³
- xx. In state and national data, a temporal relationship also has been documented between increased distribution of prescription opioids and increased mortality, in the CDC and Ohio data, as referenced above.¹²³⁴
- xxi. *Temporality* also exists with respect to the Gateway Effect, as documented by undisputed evidence that increased use and misuse of prescription opioids preceded the second and third waves of the epidemic involving the transition from prescription opioids to heroin and fentanyl. Muhuri and others documented the fact that 70-80% of recent heroin users had previously used prescription opioids.¹²³⁵ McCabe, Lankenau and Mars all demonstrated that this transition occurred after both medical use (pursuant to a doctor’s prescription) and nonmedical use (outside the parameters of a doctor’s prescription).¹²³⁶
- xxii. (4) *Dose-response*: “[I]f the association is one which can reveal a biological gradient, or dose-response curve, then we should look most

¹²³² Schroeder, et al., Association of Opioid Prescriptions from Dental Clinicians for US Adolescents and Young Adults with Subsequent Opioid Use and Abuse. *JAMA Internal Medicine* 2018; doi:10.1001/jamainternmed.2018.5419, at E5.

¹²³³ *Id.*, at E3-E4.

¹²³⁴ Similarly, in the 1964 Surgeon General’s Advisory Committee Report on Smoking and Health, the increase in lung cancer was observed in the context of large increases in exposure to cigarettes: “Nearly 70 million people in the United States consume tobacco regularly. Cigarette consumption in the United States has increased markedly since the turn of the Century, when per capita consumption was less than 50 cigarettes per year,” and cigarette consumption rose from 138 per person in 1910 to a “peak of 3,986 [per person] in 1961.” 1964 Surgeon General’s Report, fn.1136 above, at 26. This stark increase in tobacco consumption has a parallel in the large-scale increased distribution of opioids between the 1990s and 2012, with only a modest decline since that time.

¹²³⁵ Report, above, at C.9.i.

¹²³⁶ Report, above, at C.9.i.

carefully for such evidence. For instance, the fact that the death rate from cancer of the lung rises linearly with the number of cigarettes smoked daily, adds a very great deal to the simpler evidence that cigarette smokers have a higher death rate than non-smokers.”¹²³⁷

- xxiii. Numerous studies cited above provide clear and convincing evidence of a dose-response relationship, including but not limited to Edlund, Dunn, Bohnert, and Papadomanolakis-Pakis, all of which found increased risk of either opioid addiction or overdose with greater exposure to prescription opioids.
- xxiv. An analogous result is found with regard to the “Gateway Effect,” in that more frequent misuse of prescription opioids is associated with a higher rate of transition to heroin.¹²³⁸ A CDC publication similarly reported, “Drug abuse and overdose rates increased with longer use,”¹²³⁹ and another CDC publication simply stated: “Higher Dosage, Higher Risk,”¹²⁴⁰ neatly summarizing the evidence of a dose-response relationship between prescription opioids and overdose.
- xxv. Dose-response was also found in a study reporting that odds of overdose were significantly greater with increasing amounts of opioids dispensed to family members (>0-<50 morphine milligram equivalents per day: OR, 2.71 [95% CI, 2.42-3.03]; 50-<90 morphine milligram equivalents per day: OR, 7.80 [95% CI, 3.63-16.78]; ≥90 morphine milligram equivalents per day: OR, 15.08 [95% CI, 8.66-26.27]).¹²⁴¹ These findings are of particular importance in demonstrating the causal relationship between oversupply and opioid overdose, since overprescribing provides a source for excess opioid pills that are diverted from the original recipient to family members who suffer the adverse effects.
- xxvi. *Dose-response* has similarly been shown with respect to promotion, sale and distribution of opioids. In the Hadland studies described previously, the authors explicitly stated that their data showed a dose-response relationship between opioid manufacturers’ marketing and the occurrence

¹²³⁷ Hill AB, The Environment and Disease: Association or Causation? *Proceedings of the Royal Society of Medicine*. 1965;58(5), at 298. (emphasis in original). See also, 1964 Surgeon General’s Report, at 35: “The death rates increase with the amount smoked.”

¹²³⁸ Jones CM, Heroin use and heroin use risk behaviors among nonmedical users of prescription opioid pain relievers – United States, 2002-2004 and 2008-2010. *Drug Alcohol Depend*. 2013;132(1-2):95-100, at 95.

¹²³⁹ Paulozzi LJ, et al. Risk of Adverse Health Outcomes with Increasing Duration and Regularity of Opioid Therapy. *J Am Board Fam Med*. 2014 ; 27(3): 329–338, at p. 329. doi:10.3122/jabfm.2014.03.130290, at 329.

¹²⁴⁰ Centers for Disease Control and Prevention, Calculating Total Daily Dose of Opioids for Safer Dosage. https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf, at 1.

¹²⁴¹ Khan, et al., Association of Opioid Overdose with Opioid Prescriptions to Family Members. *JAMA Internal Medicine* (2019), doi:10.1001/jamainternmed.2019.1064, at E-3.

of opioid prescribing, with each additional industry-sponsored meal associated with additional opioid prescribing.¹²⁴²

- xxvii. ARCOS data on opioid sales also strongly support Dose-response on a population scale. “Death rates from opioids soared in the towns, cities and counties that were saturated with billions of prescription pain pills from 2006 through 2012, according to government death data and a previously undisclosed database of opioid shipments made public this week. ... The national death rate from opioids was 4.6 deaths per 100,000 residents. But the counties that had the most pills distributed per person experienced more than three times that rate on average.”¹²⁴³ My colleague at Stanford, Keith Humphreys, who served as a drug policy adviser to the George W. Bush and Obama administrations, “said the correlation of opioid deaths and pain pill distribution could be expected. ‘These horrible death rates should not surprise anyone,’ Humphreys said. ‘The supply of drugs matters enormously no matter what else we try to do. When there’s a flood of addictive drugs, lots of people end up being harmed’.”¹²⁴⁴
- xxviii. A further example of *dose-response* at the population level is found in a 2019 study by Ghertner, documenting the relationship between opioid sales (ARCOS data) with county-level opioid-related hospitalization rates. Ghertner reported that there was a 9% increase in opioid-related hospitalizations for each one morphine kilogram equivalent increase in opioid sales.¹²⁴⁵ This study further documents that the *Dose-response* factor is operative at both the personal and population levels, with respect to individual exposures as well as widespread promotion and distribution to the nation as a whole.
- xxix. (6) *Plausibility*: “Biological plausibility is not an easy criterion to use and depends upon existing knowledge about the mechanisms by which the disease develops. When biological plausibility exists, it lends credence to an inference of causality.”¹²⁴⁶
- xxx. In this case, biological plausibility of prescription opioids as the cause of the various harms described in this Report has been established by the evidence detailed in Sections §B.1 and §B2, above. In summary, the

¹²⁴² Hadland SE, *et al.* In Reply. *JAMA*. 2018;178(10):1426-1427 at 1426.

¹²⁴³ Horwitz, et al. Opioid death rates soared in communities where pain pills flowed. (July 17, 2019) https://www.washingtonpost.com/investigations/opioid-death-rates-soared-in-communities-where-pain-pills-flowed/2019/07/17/f3595da4-a8a4-11e9-a3a6-ab670962db05_story.html, at 1 (emphasis added).

¹²⁴⁴ *Id.*, at 4 (emphasis added). To the best of my knowledge, Professor Humphreys is not a retained witness in any opioid litigation.

¹²⁴⁵ Ghertner, R. U.S. county prevalence of retail prescription opioid sales and opioid-related hospitalizations from 2011 to 2014. *Drug Alcohol Depend.* 2019;194:330-335. doi:<https://doi.org/10.1016/j.drugalcdep.2018.10.031>, at 330.

¹²⁴⁶ Federal Judicial Center, *Reference Manual on Scientific Evidence*, 3rd edition, 2011, at 604.

molecular similarity between prescription opioids and heroin, the impact of these molecules on the dopamine system and the development of the disease of addiction, and their effects on respiratory suppression (slowed breathing) and bradycardia (lowered heart rate) as the cause of overdose death, are well-documented and established. It is similarly well-known that the phenomenon of tolerance is common, requiring prescription opioid users to increase the dose to achieve the same effect, thereby increasing the risk in accordance with the dose-response effects documented above.

- xxxi. *Experiment:* As mentioned above, this factor refers to the effects of prevention or cessation of exposure in reducing disease. CDC data show that “Opioid prescribing has declined substantially across the United States between 2014 and 2017,”¹²⁴⁷ and that prescription opioid-involved overdose death rates decreased by 13.5% from 2017-2018.¹²⁴⁸ Also, a recent Continuing Medical Education publication stated, “Patients with opioid problems may have extended periods of abstinence and usually do well. However, there is a chronic risk of accidental overdose, trauma, suicide, and infectious diseases. *The risk decreases with abstinence from opioids.*”¹²⁴⁹
- xxxii. *Summary:* According to the generally accepted methods described above, it is clear that widespread sale and distribution of prescription opioids has resulted in exposures that are causally related to the epidemics of fatal and non-fatal opioid overdose, opioid addiction, and transition to illicit opioid use.

14. For the reasons explained, the Pharmaceutical Opioid Industry bears responsibility for the misrepresentation of safety and efficacy, the ubiquitous distribution of prescription opioids, and the unchecked dispensing of prescription opioids, which resulted in the ongoing epidemic. To the extent that other factors contributed, those conditions were exploited by the Industry to increase the extent of harm.

- a. As I wrote in my book, *Drug Dealer, MD*,¹²⁵⁰ doctors were “duped” by the myths that the risk of addiction to prescription opioids was “rare,” and that the drugs were beneficial for chronic pain. I also wrote at that time, and I continue to hold the opinion, that others had some responsibility for the opioid epidemic.

¹²⁴⁷ Kuehn B. (2019). Declining Opioid Prescriptions. *JAMA*, 321(8), 736. <https://doi.org/10.1001/jama.2019.0647>

¹²⁴⁸ Centers for Disease Control and Prevention, Press Release, New Data Show Significant Changes in Drug Overdose Deaths (March 18, 2020) <https://www.cdc.gov/media/releases/2020/p0318-data-show-changes-overdose-deaths.html>

¹²⁴⁹ Dydyk, A. M., Jain, N. K., & Gupta, M. (2020). Opioid Use Disorder. <https://www.ncbi.nlm.nih.gov/books/NBK553166>, at 2 (emphasis added).

¹²⁵⁰ Lembke, “*Drug Dealer, MD*,” fn. 2, above.

- b. The Food and Drug Administration (FDA) is an agency within the U.S. Department of Health and Human Services responsible for assuring the safety, effectiveness, and quality of medical drugs. It is responsible for approving drugs before they reach the market, and monitoring the safety and marketing of those drugs after they are publicly available. In my book, *Drug Dealer, MD*, I assigned some responsibility for the prescription drug epidemic to the FDA, and to the Defendants for efforts to influence the FDA.¹²⁵¹
- c. The Toyota-ization of Medicine
 - i. The majority of doctors today work in large integrated health care systems. During the 1990s and 2000s, there occurred a mass migration of doctors out of private practice and into managed care organizations. In 2002, 70% of U.S. physician practices were physician-owned. By 2008, more than 50% of U.S. physician practices were owned and operated by hospitals or integrated health delivery systems, and that number continues to rise.¹²⁵²
 - ii. The migration of doctors into integrated health care systems (hospital factories) has transformed medical treatment. Doctors work much less autonomously. Treatment options are often dictated by hospital administrators, guidelines (*see* Joint Commission, §4.h, above), and third-party payers (health insurance companies). The result is that doctors experience enormous pressure to get patients in and out quickly, to palliate pain, and to have “satisfied customers.” This too has contributed to the problem of overprescribing.¹²⁵³
 - iii. These structural factors opened the doors, but the aggressive misrepresentation of risks and benefits took advantage of these conditions to maximize sales and maximize harm.
- d. I have also written, in *Drug Dealer, MD*, about the manipulative behaviors of patients in attempting to obtain opioid drugs from their doctors. These behaviors are not surprising; in fact, they are diagnostic of the disease of addiction, whether the drug is OxyContin, or Opana, or heroin. In my opinion, the Pharmaceutical Opioid Industry has attempted to blame victims of the disease of addiction for the epidemic resulting from their own misleading statements regarding their dangerously addictive drugs, while at the same time promoting the false message

¹²⁵¹ Lembke, “*Drug Dealer, MD*,” fn. 2, above; Fauber J. FDA and Pharma: Emails Raise Pay-for-Play Concerns. *Sentinal/MedPage Today*. October 7, 2003, *see* <http://www.medpagetoday.com/PainManagement/PainManagement/42103>, at p. 1.

¹²⁵² Kocher R, Sahni N. Hospitals ‘ Race to Employ Physicians — The Logic Behind a Money Losing Proposition. *N Engl J Med*. 2011;1790-1793, at p. 1791.

¹²⁵³ Lembke A. Why Doctors Prescribe Opioids to Known Opioid Abusers. *N Engl J Med*. 2012;367(17):1580-1581.

that patients taking these drugs for pain under a doctor's prescription have little or no risk of addiction or overdose.

- e. An article published in *Science* in 2018 by Jalal, *et al.*, "Changing Dynamics of the Drug Overdose Epidemic in the United States from 1979-2016,"¹²⁵⁴ suggests that mortality data from numerous "drug-specific subepidemics" can be fitted to a smooth exponential curve during that time period. However, the authors note the "paradox" presented by these results, since the data combine mortality associated with subepidemics as disparate as heroin and fentanyl deaths in the northeastern United States with methamphetamines in the southwestern states.¹²⁵⁵ Accordingly, an after-the-fact fitting of 38 years of combined data to a smooth curve does not obviate the need to understand each subepidemic on its own terms. In the case of prescription opioids, factors relevant to that epidemic have been addressed throughout this report, and are summarized as follows:
 - i. The apparent continuity of the overdose mortality rate curve in the Jalal *et al.* article, on closer inspection, shows a definitive rise above the smooth curve between 2001 and 2010, corresponding to the prescription opioid epidemic.¹²⁵⁶
 - ii. A study by Segel *et al.* demonstrates that the prescription opioid epidemic that incited the broader opioid epidemic, has also contributed to the fourth wave of the epidemic involving a rise in sedative and stimulant overdose deaths.¹²⁵⁷
 - iii. The problem of addiction more broadly in society and culture today does not negate the significant role of opioids manufacturers and distributors in causing this epidemic. The misrepresentations of risks and benefits and the oversupply of prescription opioids through the distribution chain were essential contributing factors to the resulting epidemic.
 - iv. Although forces may be operative to accelerate demand, such as despair, loss of purpose, and dissolution of communities, studies show that the 'push' of increased access to opioids has played a bigger role than the 'pull' of despair.¹²⁵⁸
 - v. Oversupply of prescription opioids is associated with increased opioid-related mortality. Approximately 86 billion oxycodone and hydrocodone pills were delivered to US pharmacies from 2006 to 2013 and per capita

¹²⁵⁴ Jalal H, Buchanich JM, Roberts MS, Balmert LC, Zhang K, Burke DS. Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016. *Science*. 2018. doi:10.1126/science.aau1184.

¹²⁵⁵ *Id.* at p. 1.

¹²⁵⁶ *Id.*

¹²⁵⁷ Segel, "Persistence and Pervasiveness", fn. 1074, above, at p. 1.

¹²⁵⁸ Ruhm, *et al.*, "Deaths of Despair," fn. 1136, above.

pill volume (“PCPV”) has been positively associated with opioid-related deaths (“ORDs”), so that “each one-pill increase in PCPV was associated with 0.20 additional ORDs within the following three years.”¹²⁵⁹ Griffith *et al.* further found that “even after accounting for various confounding factors, counties with particularly high PCPV experienced substantially more (16,436) ORDs than counties with below-median PCPV. On a national level, these excess deaths equate to approximately 11.1% of all ORDs recorded from 2006 to 2013”.¹²⁶⁰

15. Ending the epidemic of opioid addiction, dependence, and death will require significant investment of resources. An effective strategy will be multifaceted, and will accomplish the following: prevent new cases of addiction, dependence, and death (primary prevention), limit progression of harm (secondary prevention), and treat existing cases (treatment). These changes will require curbing opioid prescribing, re-educating patients and health care providers, creating de-prescribing clinics, promoting naloxone and other harm-reduction strategies, and building an enduring medical infrastructure to treat addiction.

- a. Primary prevention: Preventing new cases of the disease by limiting access to opioids, re-educating prescribers, and rebuilding communities devastated by the epidemic.
 - i. Opioids should not be prescribed as first line treatment for most forms of pain. Exceptions include cases of severe tissue injury, peri-operatively when multimodal analgesia is insufficient, and as palliative/end of life care.
 - A. For acute pain, the CDC guidelines recommend no more than 3 to 7 days of opioid treatment. Even within this general guideline, it is important to limit both the dose and frequency of administration of opioid drugs during the 3-7 day window, to minimize the increase in long-term use that has been documented following higher doses of opioids for acute pain, and to limit the diversion of unused pills.
 - B. First line treatment for pain should include non-opioid medications and non-medication treatment for pain (non-opioid medications, physical therapy, psychotherapy). The latter are especially important for the treatment of chronic pain.¹²⁶¹
 - C. There may be unusual instances when opioid medications can be used to good effect in the treatment of chronic pain; but even in this setting, avoiding daily use to avoid tolerance and dependence

¹²⁵⁹ Griffith KN, *et al.* Implications of county-level variation in US opioid distribution. *Drug and Alcohol Dependence*. 2021;219:1-7, at p.3.

¹²⁶⁰ *Id.*, at p. 4.

¹²⁶¹ Delgado, *et al.*, “National Variation,” fn. 1080, above, at p. 389.

is recommended. Further, very close monitoring for the emergence of adverse medical consequences, including misuse and addiction, using objective criteria such as urine toxicology and database scrutiny, are essential components of a safe and effective treatment plan. Further, an exit strategy for cessation of opioid therapy is necessary, should risks outweigh benefits at any point in the treatment, in recognition that most patients will have become dependent and will taper with difficulty.¹²⁶²

- ii. Data on the impact of interventions to curb opioid prescribing have recently become available supporting the view that limiting opioid prescribing in a systematic way reduces prescription opioid-related overdose deaths without adversely compromising pain treatment.
 - A. Massachusetts had the first of its kind state-wide acute care prescribing limits and a required-check of the Prescription Drug Monitoring Programs (PDMPs) prior to opioid prescribing. As a result it reduced opioid prescriptions by 30%.¹²⁶³
 - B. The Department of Public Health determines mean and median quantity and volume of prescriptions for opioids, within categories of similar specialty or practice types. Prescribers who exceed mean or median will be sent notice.¹²⁶⁴
 - C. The law establishes a drug stewardship program to be paid for by drug companies that makes it easier for patients to safely dispose of unwanted and unused medications. Effective Jan. 1, 2017.¹²⁶⁵
 - D. The State of Massachusetts has launched core competencies for safe prescribing of opioids in the state's medical schools, community health centers, nursing, physician assistant, dental schools and schools of social work."¹²⁶⁶ Commensurate with decreases in opioid prescribing, Massachusetts has seen a decrease in opioid-related overdose deaths: "Opioid-related overdose deaths in Massachusetts have fallen steadily over the past three quarters even as the presence of fentanyl in overdose deaths reached an all-time high....Overall in 2017 there was a 4 percent decrease in

¹²⁶² Dunn, *et al.*, "Opioid Prescriptions," fn. 1171, above, at p. 86.

¹²⁶³ Sandoe, E., *et al.*, "Policy Levers That States Can Use to Improve Opioid Addiction Treatment And Address the Opioid Epidemic", Health Affairs Blog. (Oct. 2, 2018). <https://www.healthaffairs.org/doi/10.1377/hblog20180927.51221/full/>.

¹²⁶⁴ *Id.*

¹²⁶⁵ *Id.*

¹²⁶⁶ Massachusetts Department of Public Health Press Release, "Year Over Year Opioid-Related Overdose Deaths Decline in Massachusetts; Opioid Prescriptions Fall 30 Percent", August 24, 2018. See <https://www.mass.gov/news/year-over-year-opioid-related-overdose-deaths-decline-in-massachusetts-opioid-prescriptions>, at p. 3 (emphasis in original)

opioid-related overdose deaths from 2016. The data also shows that the Commonwealth has experienced a 30 percent decline in opioid prescriptions since the launch of the Massachusetts Prescription Monitoring Program (MassPAT) in August 2016.¹²⁶⁷

- E. A successful program in Chittenden County, Vermont achieved a 50% decline in opioid mortality through a multi-faceted program that included an increased capacity “hub” (the County) and increased number of physicians treating opioid addiction (the “spokes”); a Safe Recovery syringe exchange center and low-barrier sites for buprenorphine treatment; and support for a recent statute requiring such medications to be provided to prisoners with addiction treatment.¹²⁶⁸

■ As noted previously, an article in the *New England Journal of Medicine* in 2010 included the comment that prescription opioids are “essentially legal heroin” as well as a comment as to how the FDA should revise a Risk Evaluation and Management Strategy (REMS) for use of opioids, a FDA Advisory Board member stated, “We need to think about how we would construct a REMS if we were going to be marketing heroin.”¹²⁶⁹ I agree with these statements, since prescription opioids are as addictive as heroin and operate on the same neuro-circuitry in the same manner. Current REMS training is insufficient to educate prescribers about the risks of opioids. We need more comprehensive prescriber training on the evidence of benefits and harms with opioids for medical use, how to monitor patients taking opioids for medical use, how to taper patients off opioids, and how to intervene when a problem arises.

- iv. Medical and nursing schools across the country are beginning to implement addiction medicine curricula, an essential part of the reform process to combat this epidemic. I have led an initiative here at Stanford University School of Medicine to create our first ever addiction medicine curriculum since 2017, and I am involved in promoting similar initiatives across the country.

- A. As explained at paragraph 26, above, I have been asked to “re-educate” doctors in many jurisdictions, to correct misinformation and provide accurate data on the significant risks and minimal benefits of opioid therapy, particularly for chronic pain. Such re-education is designed to reduce or eliminate over-prescribing of

¹²⁶⁷ *Id.*, at p. 1.

¹²⁶⁸ City of Burlington, Mayor’s Office, Press Release, “Mayor Miro Weinberger and Community Partners Announce 50 Percent Decline in Opioid-Related Overdose Fatalities in Chittenden County in 2018 (Feb. 14, 2019), <https://www.burlingtonvt.gov/Press/mayor-miro-weinberger-and-community-partners-announce-50-percent-decline-in-opioid-related>.

¹²⁶⁹ Okie, “A flood of opioids”, fn. 846, above, at p. 1981.

opioids, and thereby reduce or eliminate the panoply of ill effects that they cause

- B. I testified at a White House symposium¹²⁷⁰ on the importance of educating health care providers on addiction treatment and safe prescribing. At that symposium, I suggested a school loan repayment program to incentivize health care providers to treat addiction in underserved areas after completing their training. This suggestion was taken up by Representative Clark and Representative Rogers as the Substance Use Disorder Workforce Loan Repayment Bill, which was included as a key provision in the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act, also known as the SUPPORT Act, passed September 28, 2018. Although the legislation was approved, there is yet to be a source of funding.
- C. I am the Program Director for Stanford's Addiction Medicine Fellowship, a one-year fellowship to provide advanced training in addiction medicine. I also work on a national level to promote these fellowships, and was the inaugural president of the Addiction Medicine Fellowship Directors' Association (AMFDA).
- D. I have authored articles on the importance of teaching addiction medicine to medical students, residents, and fellows, including "The Opioid Epidemic as a Watershed Moment for Physician Training in Addiction Medicine" (Academic Psychiatry, 2018)¹²⁷¹ and "Qualitative Assessment of Clerkship Students' Perspectives of the Topics of Pain and Addiction in their Preclinical Curriculum" (Academic Psychiatry 2018).¹²⁷² In these articles, I address the need for more robust training in the screening and intervention of patients with the full spectrum of opioid use disorders (including misuse and dependence). I further recommend increasing medical school hours of training in addiction medicine, including safe prescribing of controlled substances.
- v. Consider prohibiting the pharmaceutical industry from funding or influencing Continuing Medical Education (CME) courses for prescribers.

¹²⁷⁰ The Addiction Medicine Foundation, "Congressional Briefing – Addiction Medicine: The Urgent Need for Trained Physicians" (Sep. 28, 2017), https://www.youtube.com/watch?v=y6kBoQckmHw_

¹²⁷¹ Lembke A, Humphreys K. The Opioid Epidemic as a Watershed Moment for Physician Training in Addiction Medicine. *Acad Psychiatry*. 2018;42(2):269-272. doi:10.1007/s40596-018-0892-8.

¹²⁷² Raber I, Ball A, Papac J, Lembke A, *et al*. Qualitative Assessment of Clerkship Students' Perspectives of the Topics of Pain and Addiction in their Preclinical Curriculum. *Acad Psychiatry*. 2018;42(5):664-667.

- vi. Consider promoting CME education that explicitly eschews industry funds and influence, and providing academic detailing (unbiased, evidence based information for prescribers).
 - vii. Earmark money to provide medical school, residency, and fellowship training in addiction treatment.
- b. Secondary prevention: limit progression of harm by helping patients on dangerously high doses come down or off of opioids, independent of whether they are addicted, and by implementing harm reduction strategies to mitigate the dangers of opioids.
- i. To accomplish effective, safe, and compassionate opioid tapers in this country, we need funding to build de-prescribing clinics to provide treatment for opioid dependent patients. Where de-prescribing clinics are not feasible, we need to embed an interdisciplinary, chronic care treatment team inside of primary care to support deprescribing/opioid tapering. This chronic care team would consist of physicians, nurses, social workers, case workers, psychologists, and others trained to help patients manage the physically and emotionally taxing process of decreasing prescribed opioids. Primary care doctors, already overloaded with responsibilities, are unlikely to achieve successful tapers in opioid dependent, high dose legacy patients, without significant incentives and support. This will require an enormous investment of resources, as it is estimated that millions of Americans are dependent on opioids and suffering from or at heightened risk for adverse consequences.
 - ii. I worked with colleagues at Stanford to develop a protocol for helping opioid dependent patients compassionately and safely taper down or off of prescribed opioids: “The BRAVO Protocol.” The protocol has been adopted by the Oregon Pain Guidance, the Oregon Pain Task Force, and has influenced other opioid task forces around the country who are struggling with the problem of opioid dependent (but not addicted) chronic pain patients.¹²⁷³
 - iii. We have created a free online continuing medical education course - “The BRAVO Protocol: How to Taper Patients Off of Chronic Opioid Therapy.” This course, created in conjunction with the Stanford continuing medical education office, teaches prescribers how to safely and compassionately taper opioids, something that is not currently taught in medical schools.

¹²⁷³ Oregon Health Authority Oregon Opioid Taper Guidelines Task Force Resources.
<https://www.oregon.gov/oha/PH/PreventionWellness/SubstanceUse/Opioids/Documents/taskforce/tapering-taskforce/2019-Opioid-Taper-Task-Force-Resources.pdf>.

- iv. As mentioned above (§A¶24), our tapering protocol was endorsed by the United States Department of Health and Human Services in 2019, and it became the subject of a Continuing Medical Education course in 2020. The course has also been positively featured in the lay press, highlighting that it features the first-person account of a patient who was, with support, able to taper off of opioids and experienced improved chronic pain as a result.¹²⁷⁴ We have created a companion page summarizing The BRAVO Protocol, which has gained wide informal distribution among prescribers. It summarizes the key learning points as below. (See BRAVO Protocol summary attached to this report.) The bottom line is, helping patients to decrease or discontinue long term opioid therapy presents a challenging clinical scenario, especially in patients on high doses (greater than 80 MEDs), with moderate to severe chronic pain, and co-occurring mental health disorders (depression, anxiety, PTSD). For this type of complex chronic pain patient, the usual recommendation to decrease opioids by 10% of the starting dose every week frequently will not apply. These patients often need slower tapers on the order of 5-10% decreases or less every month. Expert consensus suggests the taper speed should be tailored to the individual needs of the patient. Some patients who have been on opioids for years to decades, may require *years* to taper their dose. With this complex chronic pain patient in mind, the BRAVO protocol outlines a safe and compassionate strategy to approach opioid tapering, while also maintaining a therapeutic alliance between the treatment team and each patient.
 - v. Other harm reduction strategies include increasing naloxone distribution, promoting clean needle exchanges, improving patient education regarding safe medication storage and appropriate disposal of excess medications, and increasing public awareness of poison center services.
- c. Treatment
- i. We need a robust infrastructure to treat addiction, both within and outside the traditional sources for medical care. Such an infrastructure does not currently exist. Instead what we have are siloes of care with limited and contingent funding, or treatment centers accessible only by the rich.
 - ii. Addiction treatment should be offered within every hospital, clinic, emergency room, jail, drug court, etc., across America. “Meeting patients where they are” has become a mantra for the field. Patients with this complex behavioral illness are more likely to engage in treatment when they are offered treatment in settings where they are frequently found, like in hospitals, emergency rooms, jails, and even in settings where they

¹²⁷⁴ Parloff R. Tapering off long-term Rx opioids: a first-hand account, Opioid Institute. (Oct. 15, 2018), <https://opioidinstitute.org/2018/10/15/tapering-opioids-lembke/>. (last accessed January 15, 2019)

might be using drugs (such as at the site of first responders, clean needle exchange sites, safe consumption sites, etc.).

- An effective addiction treatment infrastructure should be based on evidence-based treatments for addiction, including buprenorphine, methadone maintenance, and naltrexone. Opioid agonist therapy (buprenorphine or methadone maintenance) has one of the most robust evidence bases of any addiction treatment. Multiple placebo controlled trials over many decades have demonstrated the efficacy of opioid agonist therapy in the treatment of opioid use disorder.¹²⁷⁵
- iv. Addiction is a chronic relapsing and remitting disorder, requiring a chronic care model and a team based approach, including a peer recovery coach, care coordinator, behavioral health specialist, licensed counselor, and a primary care professional.¹²⁷⁶ One way to address this problem within our current health care system, is to co-locate behavioral health specialists within primary care, or create a hub and spoke model with specialty clinics providing support to primary care clinics. A concurrent strategy is to build Centers of Excellence for Addiction Treatment at every major medical center around the country, similar to existing Centers of Excellence for cancer, cardiac disease, and diabetes.
- As a chronic illness, addiction can require lifelong treatment. In my clinical experience, most people with moderate to severe opioid use disorder struggle to some degree to remain abstinent for the rest of their lives and there is a high rate of relapse when individuals go off of MAT (Medication-Assisted Treatment). Thus, the abatement plan to address the opioid epidemic should focus on providing the maximum level of both MAT and non-MAT resources possible, as quickly as possible, and should maintain this level of treatment long-term, as contemplated in the proposed abatement plan.
- vi. A successful treatment system would allow for those with the disease to titrate their treatment based on illness severity over time, with the recognition that the normal course of addiction involves periods of remission and recurrence, just like cancer.
- vii. Addiction treatment and recovery requires intensive individual and/or group therapy interventions, which should be integrated into treatment alongside medications.

¹²⁷⁵ Strang J, Babor T, Caulkins J, Fischer B, Foxcroft D, Humphreys K. Drug policy and the public good: evidence for effective interventions. *Lancet*. 2012;379(9810):71-83, at p. 78.

¹²⁷⁶ “The Addiction Recovery Medical Home As An Alternative Payment Model,” Health Affairs Blog, December 12, 2018. DOI: 10.1377/hblog20181211.111071. *Heal Aff Blog*. doi: 10.1377/hblog20181211.111071, at p. 3.

- viii. Mutual help groups such as Narcotics Anonymous have a long tradition of aiding people with addiction achieve and maintain recovery. New models employing peer counselors as part of an interdisciplinary medical team to treat and target addiction, are being investigated. These models should be considered as a way to bridge inpatient and outpatient treatment and sustain recovery as patients return to their normal lives. Undergirding the creation of a robust infrastructure to target and treat addiction, is the need for a trained workforce to deliver this care.

D. Conclusion

Addiction is a chronic, relapsing and remitting disease with a behavioral component, characterized by neuroadaptive brain changes resulting from exposure to addictive drugs. One of the biggest risk factors for addiction is simple access to addictive drugs. When supply of an addictive drug is increased, more people become addicted to and suffer the harms of that drug. The Defendants' conduct in promoting increased supply and widespread access to prescription opioids, including through misleading messaging, has resulted in an epidemic of opioid addiction and overdose death. Increased supply contributed to more pain patients becoming addicted to opioids, including those who turned from prescription opioids to illicit sources of opioids such as heroin (The Gateway Effect). Increased supply contributed to more pain patients and newborns becoming dependent on opioids, increasing their risk for opioid-related morbidity and mortality (The Dependence Effect). Increased supply contributed to more diversion of prescription opioids, causing a dramatic increase in the widespread availability of opioids to persons for whom they had not been prescribed (The Tsunami Effect). The increased supply of prescription opioids through licit and illicit sources resulted in a prescription opioid epidemic in the United States. Others bear some lesser responsibility for the opioid epidemic. However, today's opioid crisis would not have occurred without the paradigm shift encouraged by the Pharmaceutical Opioid Industry, whose actions resulted in the overprescribing and excessive distribution and dispensing of prescription opioids. In a *New England Journal of Medicine* commentary regarding the CDC Opioid-Prescribing Guideline, CDC physicians Thomas Frieden and Debra Houry stated, "We know of no other medication routinely used for a nonfatal condition that kills patients so frequently."¹²⁷⁷

Ending the epidemic of opioid addiction, dependence, and death will require significant investment of resources. An effective strategy will be multifaceted and will accomplish the following: prevent new cases of addiction, dependence, and death (primary prevention), limit progression of harm (secondary prevention), and treat existing cases (treatment).

¹²⁷⁷ Frieden TR, Houry D. Reducing the Risks of Relief — The CDC Opioid-Prescribing Guideline. *N Engl J Med*. 2016. doi:10.1056/nejmp1515917, at p. 1503.

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Exhibits to this Report:

Attached as Exhibit A is a copy of my current curriculum vitae and a list of all publications authored by me in the past 10 years.


Attached as Exhibit B is a list of data or other information considered by me in forming the opinions expressed herein.

Attached as Exhibit C is a statement of my compensation for services performed in this case.

Attached as Exhibit D is a list of all cases in which I have testified as an expert at trial or by deposition during the past four years.

Pursuant to 28 U.S.C. S 1746, I declare under penalty of perjury that the foregoing is true and correct.

Executed on: April 16, 2021



Anna Lembke, M.D.

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Anna Lembke, M.D. Report

EXHIBIT A

Curriculum Vitae and List of Publications

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Anna Lembke, M.D.

Professor of Psychiatry and Behavioral Sciences (Primary Appointment)
Anesthesiology and Pain Medicine (Courtesy Appointment)
Stanford University School of Medicine
Department of Psychiatry and Behavioral Sciences
401 Quarry Road, Stanford, CA, 94305
Office: 650 725-9570 Fax: 650 725-8048
alembke@stanford.edu
Last updated (March 23, 2021)

Education and Training

1985-1989	Yale University (BA, Humanities; <i>summa cum laude</i>) New Haven, CT
1989-1990	University of Beijing (Mandarin Chinese) Beijing, China
1992-1995	Stanford University School of Medicine (MD) Stanford, CA
1995-1997	Residency, Pathology Stanford University School of Medicine, Stanford, CA
1997-1998	Internship, Internal Medicine Highland Hospital, Alameda, CA
1998-2000	Residency, Psychiatry Stanford University School of Medicine, Stanford, CA
2000-2002	Fellowship in Mood Disorders, Psychiatry and Behavioral Sciences Stanford University School of Medicine, Stanford, CA

Honors and Awards

1989	<i>Summa cum laude</i> in Humanities Yale University
1989	Outstanding Contributor to Community Life Yale University
1989	Yale-China Fellowship Yale University
1995	Outstanding Teacher in Structural Biology Stanford University School of Medicine

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1999	Outstanding Research in Severe Mental Illness Janssen Scholar
2000	Travel Scholarship Medical Education and Research Foundation (MERF)
2000	Outstanding Research in Severe Mental Illness American Psychiatric Association
2002	Laughlin Fellowship American College of Psychiatrists
2009	Travel Scholarship Alcohol Medical Scholars Program
2011	Travel Scholarship Association of Medical Education, Research, Substance Abuse
2013	Faculty Fellowship Stanford University School of Medicine
2014	Excellence in Academic Teaching Stanford University School of Medicine
2015	Chairman's Clinical Innovation Award Stanford University School of Medicine
2017	Distinguished Visiting Professorship Johns Hopkins Bayview, Department of Internal Medicine
2018	Distinguished Flexner's Dean Lecturer Vanderbilt University School of Medicine
2018	Distinguished Marcel Malden Lecturer Tacoma, Washington
2018	Distinguished Alpha Omega Alpha Visiting Professorship University of Kansas School of Medicine
2018	Distinguished Alumni Award Evanston Township High School, Evanston, IL
2018	Excellence in Academic Teaching Award Stanford University School of Medicine

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- 2019 Distinguished Baldwin Lecturer
The Accreditation Council for Graduate Medical Education (ACGME)
- 2019 Distinguished Tector Lecturer
69th Annual Course for Family Physicians, Montreal, Canada
- 2019 Distinguished James Platt White Memorial Lecturer
Buffalo, New York OB/GYN Society
- 2019 Distinguished Crowley Lecturer
Lucile Packard Children's Hospital, Stanford University
- 2019 Distinguished University of Tampa Honors Symposium Lecturer
University of Tampa, Florida
- 2019 Distinguished Evelyn G. Keever Bioethics Day Lecturer
Eastern Virginia Medical School, Virginia
- 2020 Fellowship Training Directors Award
American Society of Addiction Medicine
- 2020 Hazelden Betty Ford Foundation Humanitarian Kelly Clark Spirit Award
Hazelden Betty Ford Foundation, Portland, Oregon
- 2020 Irma Bland MD Certificate of Excellence in Teaching Residents
American Psychiatric Association
- 2021 Distinguished Alpha Omega Alpha Visiting Professorship
University of Nevada, Reno School of Medicine

Academic and Clinical Appointments

Stanford University School of Medicine

- 2003-2010 Instructor Department
Department of Psychiatry and Behavioral Sciences (9/03-4/10)
- 2010-2017 Assistant Professor
Department of Psychiatry and Behavioral Sciences (5/10-4/17)
- 2012-present Chief, Addiction Medicine Dual Diagnosis Clinic
Department of Psychiatry and Behavioral Sciences
- 2013-present Program Director, Addiction Medicine Fellowship
Department of Psychiatry and Behavioral Sciences

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2016-present Courtesy Appointment
Department of Anesthesiology and Pain Medicine

2017-present Medical Director, Addiction Medicine
Stanford Health Care and Stanford University Hospital

2017-2021 Associate Professor
Department of Psychiatry and Behavioral Sciences (7/17-6/21)

2020-present Director, Taube Youth Addiction Initiative
Department of Psychiatry and Behavioral Sciences

2021-present Professor of Psychiatry and Behavioral Sciences
Department of Psychiatry and Behavioral Sciences

Other Previous Employment

1991-1992 Bilingual Teacher (grades K-8), State Certified in Chinese (Mandarin) Healy
Elementary School, Chicago, IL

1989-1990 English Teacher, Yali Middle School
Changsha, China

Medical Licensure and Specialty Board Certification

1995 California medical license #A62241

2003 Diplomate, American Board of Psychiatry and Neurology
Certificate #51988; recertified 2/18/2013

2012 Diplomate, American Board of Addiction Medicine
Certificate #2012288; certified 12/15/2012 -12/31/2022

2013 DEA-X waived to prescribe buprenorphine products

2021 Diplomate, American Board of Preventive Medicine; Certificate #61-17111;
certified 01/01/2021 - Exp date 12/31/2030

Educational Leadership

2003-2005 Chair, Curriculum Committee
Department of Psychiatry and Behavioral Sciences
Stanford University School of Medicine

2009-present Course Director, CME-accredited monthly Stanford seminar series for community
physicians - “Closing the Gap: Moving towards Best Practices in Psychiatry”

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- 2012-2014 Principal Organizer and Lecturer of the free Buprenorphine Certification Course and CURES registration for Stanford University
- 2013-present Program Director, Addiction Medicine Fellowship
Department of Psychiatry and Behavioral Sciences
Stanford University School of Medicine
- 2014 Expert Consultant, Alcohol and Women Task Force
Office of the Vice Provost for Student Affairs, Stanford University
- 2014-2016 Annual Medical Student Town Hall Meetings on Wellness and Professionalism
(Issues of Substance Use and Addiction)
Office of the Dean of the School of Medicine, Stanford University
- 2015-2016 Expert Consultant, Alcohol and Other Drug (AOD) Subcommittee of the Mental Health and Well-Being Advisory Committee
Stanford University
- 2016-present Chair, Addiction Medicine Task Force
Stanford University School of Medicine
(Goal: create a new curriculum for addiction/safe opioid prescribing)
- 2017-present Committee on Professionalism
Stanford University School of Medicine

Teaching and Mentoring

Stanford University School of Medicine Ongoing Lecture Series

- 2002-present Course Director, Addiction Medicine, Stanford University School of Medicine
- 2009-present Course Director, Stanford CME series “Closing the Gap in Psychiatry”
- 2012-present Course Lecturer, Substance Use Disorders, Stanford Child Psychiatry Fellowship
- 2012-present Course Lecturer, Substance Use Disorders, Stanford Palliative Care Fellowship
- 2012/’14/’16 Biennial lecture on addiction medicine to Stanford undergraduates as part of the Hum Bio Molecular and Cellular Physiology 256 seminar

Stanford University School of Medicine Clinical Supervision (weekly year round)

- | | | |
|--------------|------------------------------|-------------------------------------|
| 2002-2018 | Inpatient Psychiatry | Medical Students, Residents/Fellows |
| 2010-present | Addiction Med/Dual Dx Clinic | Medical Students, Residents/Fellows |

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2013-present Pain and Addiction Clinic

Addiction Medicine/Pain Fellows

Stanford University School of Medicine Addiction Medicine Fellows Advisor

- 2013-14 Stacie Solt, MD, Emergency Medical and Addiction Medicine, now at San Mateo Medical Center, San Mateo, CA
- 2014-15 Mitika Kanabar, MD, Family Medicine Physician and Addiction Medicine, now at Southern California Permanente Medical Group, Lancaster, CA
- 2015-16 Chinyere Ogbonna, MD, Family Medicine, Psychiatry, and Addiction Medicine, now Medical Director of Chemical Dependency Services at Kaiser Permanente, San Jose, CA
- 2016-17 Rachel Sussman, MD, Family Medicine and Addiction Medicine, now Assistant Professor at Stanford School of Medicine and Indian Health Center/O'Connor, San Jose, CA
- 2017-18 Amer Raheemullah, MD, Internal Medicine and Addiction Medicine, now Assistant Professor and Director of the Inpatient Addiction Medicine Consult Service at Stanford School of Medicine, Stanford, CA
- 2017-18 Anusha Chandrakanthan, MD, Family Medicine and Addiction Medicine, now Adjunct Clinical Assistant Professor in Addiction Medicine at Stanford University School of Medicine, Stanford, CA, and Staff Physician at Valley Homeless Health, San Jose, CA
- 2018-19 Huiqiong Deng, MD, PhD, Psychiatry and Addiction Medicine, now Assistant Professor in Addiction Medicine at Stanford University School of Medicine, Stanford, CA
- 2018-19 Michael Polignano, MD, Psychiatry and Addiction Medicine, now Assistant Professor in Addiction Medicine at Stanford University School of Medicine, Stanford, CA
- 2019-20 Ori Ben-hamou, MD, Psychiatry and Addiction Medicine, Stanford Addiction Medicine Fellowship, Stanford, CA
- 2019-20 Nathaniel Lepp, MD, Family Medicine and Addiction Medicine, Stanford Addiction Medicine Fellowship, Stanford, CA

Stanford University School of Medicine MedScholars Advisor

- 2016 MedScholar Advisor for Inbar Raber, *Qualitative Assessment of Clerkship Students' Perspectives of Pain and Addiction Curriculum at Stanford*, Stanford

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University School of Medicine, Stanford, California

- 2017 MedScholar Advisor for Alex Ball, *Developing the Addiction Curriculum at Stanford*, Stanford University School of Medicine, Stanford, California
- 2019 MedScholar Advisor for Emily Keamy-Minor, *Alcohol Screening for Patients Receiving Prescriptions for Benzodiazepines and Opioids*, Stanford University School of Medicine, Stanford, California

Stanford University School of Medicine Junior Faculty Advisor

- 2016 -2020 Faculty Advisor for Yasmin Owusu, MD in the development of the POM Curriculum for Stanford Medical Students, Stanford University School of Medicine, Stanford, California

Stanford University/Palo Alto University Dissertation/Masters Review Committees

- 2016 Dissertation Advisor and Review Committee Member for Jennifer Bielenberg, *Addiction and Stigma*, PsyD Consortium, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California
- 2017 Dissertation Chair and Review Committee Chair for Shelby Schwartz, PsyD Consortium, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California
- 2018 Dissertation Chair and Review Committee Chair for Julia Yasser, PsyD Consortium, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California
- 2020 Dissertation Committee, Sarah Krasner, *Gender Differences in Cannabis Vaporizer Use*, PsyD Consortium, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California
- 2020 Dissertation Committee, Rebecca Rothberg, *Harm Reduction and Addiction Treatment*, PsyD Consortium, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California
- 2020 Dissertation Chair and Review Committee Chair for Benjamin Greenberg, *Shared Medical Appointments for Buprenorphine Prescribing for Individuals with Opioid Use Disorder: A Qualitative Study*, PsyD Consortium, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California
- 2020 Master's Thesis Advisor for Enrique Cazares-Navarro, *Trends of Benzodiazepine Use in the United States Among Older Adults: Clinical visits that include a*

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benzodiazepine (Xanax, Valium, Klonopin) prescription have persisted between 2015 and 2019 among older adults in the continental United States, despite growing evidence of benzodiazepine harms, Community Health and Prevention, Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, California

Professional Associations

- 2011-2016 Member, Association of Medical Education and Research in Substance Abuse (AMERSA)
- 2011-present Member, American Society of Addiction Medicine (ASAM)
- 2011-present Member, California Society of Addiction Medicine (CSAM)
- 2019-present Member, American Psychiatric Association (APA)
- 2019-present American College of Academic Addiction Medicine (ACAAM)

Regional and National Service

Professional Societies and Advisory Boards and Committees

- 2012-2015 Facilitator, California Society of Addiction Medicine (CSAM) Annual Conference, San Francisco, California
- 2013-2014 Advisor, American Board of Addiction Medicine Practice Improvement and Performance Measures Action Group (PIPMAG)
- 2013-2018 Advisor, American Board of Addiction Medicine Fellowship Development Working Group
- 2013-2019 Board Member, Medical Education and Research Foundation (MERF) for the Treatment of Addiction
- 2013-2020 Member, Public Policy Committee, CSAM
- 2014-2020 Member, California Society of Addiction Medicine Education Committee
- 2014-2018 Member, California Society of Addiction Medicine Conference Planning
- 2015-2019 Board Member, California Society of Addiction Medicine
- 2015-2016 Representative, American Society of Addiction Medicine PCORI Workshop: *Long-Term Use of Opioids for Chronic Pain*

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- 2015-2017 Representative, Appointed by Governor Jerry Brown to the Research Advisory Panel of California, January 2015
- 2015-2019 Member, Public Policy Committee, American Society of Addiction Medicine
- 2015-2016 Chair, Conference Planning Committee, California Society of Addiction Medicine Annual Conference
- 2016-2017 Vice-Chair, Conference Planning Committee, California Society of Addiction Medicine Annual Conference
- 2016-2020 Member, Physicians for Responsible Opioid Prescribing (PROP)
- 2016-2018 President, Addiction Medicine Fellowship Directors Association (AMFDA)
- 2019 Advisor, Task force for The Center on Addiction (a merger between Partnership for Drug Free Kids and CASA Columbia)
- 2019-2023 Board Member, American College of Academic Addiction Medicine
- 2020-2023 Member, American College of Academic Addiction Medicine (ACAAM) Lifelong Learning and Self-Assessment Committee

Editorial Work

- 2003-2004 Guest Editor, *Academic Psychiatry*, Issue on Women in Academia
- 2013-2014 Reviewer, *How to Find Quality Addiction Treatment*, CASAColumbia
- 2014-2017 Associate Editor, *Addiction Science and Clinical Practice (ASCP)*

Ad-Hoc Manuscript/Report Review

Academic Psychiatry
Addiction
Addiction Science and Clinical Practice
Agency for Healthcare Research and Quality (AHRQ)
American Journal of Psychiatry
Annals of Internal Medicine
Archives of General Psychiatry
Asian Journal of Psychiatry
Biological Psychiatry
Bipolar Disorder
British Medical Journal
Cambridge University Press
Culture, Medicine, and Psychiatry

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Current Biomarker Findings

Drugs: Education, Prevention & Policy

Expert Opinion on Pharmacotherapy

Expert Review of Neurotherapeutics

General Hospital Psychiatry

Healthcare: The Journal of Delivery Science and Innovation

Johns Hopkins University Press

Journal of Addiction Science and Clinical Practice

Journal of Affective Disorders

Journal of the American Medical Association

Journal of Psychiatric Research

Journal of Studies on Alcohol and Drugs

Medical Journal of Australia

New England Journal of Medicine

New Recovery Community Institutions

Pain Medicine

Psychological Medicine

Rationality and Society

Sociologic Forum

Substance Abuse

Substance Use and Misuse

Current Funding

- 7/20-6/25 Funder: Health Resources and Services Administration (HRSA),
\$1,452,178, 0.1 Calendar
Title: Addiction Medicine Fellowship
Purpose: Stanford University Department of Psychiatry proposes to expand its existing Addiction Medicine Fellowship by two fellows in medically underserved communities in Santa Clara County
Role: Principal Investigator/Project Director (CoPI: Louie)
- 7/20-6/24 Funder: NIDA, \$1,050,000, 0.1 Calendar
Title: Western Node of NIDA Clinical Trials Network
Purpose: Oregon Health Sciences University, Stanford University/Palo Alto VA, UC San Francisco, and the San Francisco Health Department propose to serve as a node in NIDA's national network which generates and support randomized clinical trials of drug addiction treatment.
Role: Co-Investigator (MPI: Korthuis and Humphreys)
- 12/19-11/22 Funder: Stanford Center for Health Education ("SCHE")
Title: Psychology of Addiction and Recovery
Purpose: Stanford University Department of Psychiatry in partnership with SCHE and Getsmarker proposes to create an online professional education course on addiction medicine for learners around the world.
Role: Academic Director

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7/18-7/21 Funder: Department of Governmental Relations, Stanford Hospital/Clinics
Title: Addiction Medicine Peer Mentor Program
Purpose: To explore the feasibility and safety of integrating a peer mentor into the Addiction Medicine Dual Diagnosis Clinic Treatment Team
Role: Co-Investigator (MPI: Raheemullah and Gallagher)

Previous Funding

1/00-1/01 Funder: American Psychiatric Association and Eli Lilly Training Grant
Title: Facial Emotion Processing in Patients with Bipolar Disorder
Role: PI

7/01-7/02 Funder: National Institute of Mental Health Research Fellowship
Title: Facial and Vocal Emotion Processing in Mood Disorders
Role: PI

11/01-11/03 Funder: National Institute of Mental Health
Title: Systematic Treatment Enhancement Program for Bipolar Disorder
Role: Site-Investigator (PI: Sachs, Mass General)

12/08-12/10 Funder: National Institute of Mental Health
Title: HPA Axis in Psychotic Depression, 2 RO1 MH050604-12
Role: Co-Investigator (PI: Schatzberg)

10/09-10/14 Funder: National Institute on Drug Abuse
Title: Extended Treatment for Smoking Cessation, R01 DA017441
Role: Co-Investigator (PI: David)

7/11-7/14 Funder: National Institute of Health
Title: Genetics of Symptomatology and Treatment Response in Depression
Role: Investigator (PI: Murphy)

1/12-12/15 Funder: Michael Alan Rosen Foundation
Title: Screening and Brief Intervention for Substance Misuse/Abuse
Role: Co- PI (Co-PI: Humphreys)

11/13-11/14 Funder: Stanford Center at Peking University (SCP KU)
Title: Narratives of Addiction in Contemporary China
Role: PI

1/14-1/15 Funder: Peter F. McManus Charitable Trust, SPO #112718
Title: Exploring Physician Opioid Prescribing Using a Novel Approach to Data Mining of Medical Records
Role: PI

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- 1/14-1/15 Funder: American Board of Addiction Medicine/Conrad N. Hilton Foundation
Title: 2014 Next Generation Award for Adolescent Substance Use Prevention
Role: PI
- 11/14-11/15 Funder: Stanford Center for Continuing Medical Education (SCCME)
Title: Prescription Drug Abuse: Compassionate Care for a Complex Problem
Role: PI
- 1/15-1/16 Funder: American Board of Addiction Medicine/Conrad N. Hilton Foundation
Title: 2015 Next Generation Award for Adolescent Substance Use Prevention
Role: PI
- 7/16-7/17 Funder: Stanford Center for Continuing Medical Education (SCCME)
Title: Tapering Patients off of Chronic Opioid Therapy
Role: PI
- 11/2017 Funder: VA Center for Innovation to Implementation
Title: The Hidden Role of Benzodiazepines in the Prescription Drug Epidemic
Role: Small grant awardee
- 10/15-10/20 Funder: National Institute of Alcohol Abuse & Alcoholism
Title: CNS Deficits: Interaction of Age & Alcoholism, R01 AA005965
Purpose: Determine the impact of heavy, chronic alcohol use on brain structure and function, and the capacity of the brain to heal in a period of abstinence.
Role: Co-Investigator (MPI: Pfefferbaum and Zahr)

Scholarly Work

Books

Lembke, A. *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Johns Hopkins University Press, November 15, 2016

Lembke, A. *Dopamine Nation: Finding Balance in the Age of Indulgence*, Dutton Penguin Random House, August 2021

Peer-Reviewed Online Stanford EdX CME Courses

Lembke, A. *Prescription Drug Misuse and Addiction: Compassionate Care for a Complex Problem*, produced by the Stanford Center for Continuing Medical Education, <https://www.edx.org/bio/anna-lembke>

Lembke, A. *Tapering Patients Off of Chronic Opioid Therapy*, produced by the Stanford Center for Continuing Medical Education, <https://www.edx.org/bio/anna-lembke>

Lembke, A. *The Psychology of Addiction and Recovery*, produced by the Stanford Center for Health Education in collaboration with Getsmarter and 2u, https://sche-online.getsmarter.com/presentations/lp/stanford-sche-psychology-of-addiction-and-recovery-online-short-course/?ef_id=c:434032772062_d:c_n:g_ti:kwd-536821850850_p:_k:%2Bstanford%20%2Bpsychology_m:b_a:101946842798&gclid=EAIaIQobChMI-bif96zQ6wIVhCmzAB22uAwAEAAAYASAAEgKyQfD_BwE&gclsrc=aw.ds

Peer-Reviewed Original Research Articles

1. **Lembke A**, Ketter TA. Impaired Recognition of Facial Emotion in Mania *American Journal of Psychiatry* 2002; 159(2):302-4.
2. Menon V, Levitin DJ, Smith BK, **Lembke A**, Krasnow BD, Glazer D, Glover GH, McAdams S. Neural Correlates of Timbre Change in Harmonic Sounds *Neuroimage* 2002; 17(4):1742-54.
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Peer-Reviewed Book Chapters

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Cambridge University Press, 2007, pp 187-192

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8. Cohen, G., **Lembke, A**. Childhood Behavior and Later Substance Use, in *Encyclopedia of Drugs, Alcohol & Addictive Behavior*, 3rd Edition. Edited by Korsmeyer P and Kranzler H, Macmillan Reference USA, 2008
9. **Lembke A**, Humphreys K. Chapter 26: Substance Use Disorder Presenting as a Mood Disorder in *How To Practice Evidence Based Psychiatry: Basic Principles and Case Studies*. Edited by Taylor CB, APPI, Washington, D.C., 2009 , pp 233-246
10. **Lembke, A.**, Humphreys, K. Moos, R. Diagnosis, Development, and Treatment of Substance Use Disorders among Adolescents and Young Adults, in *Stanford School of Medicine Handbook of Developmental Psychiatry*. Edited by Steiner, H, NY, Jossey/Bass/Wiley, 2010, pp. 365-396
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17. Ogbonna C, **Lembke A.** Alcohol and substance use and co-occurring behaviors. In Roberts LW (editor). *University Student Mental Health: A Guide for Psychiatrist, Psychologists, and Leaders Serving in Higher Education*. Arlington, VA: American Psychiatric Publishing, Inc., 2018.
18. **Lembke, A.,** Raheemullah, A. Addiction and Exercise. In Noordsy DL, (editor). *Lifestyle Psychiatry: Using Exercise, Diet and Mindfulness to Manage Psychiatric Disorders*. Washington DC: American Psychiatric Publishing. (2019)

Other Publications

1. **Lembke, A.** A Psychosocial Approach to Postpartum Depression *Psychiatric Times* 2002; XIX(6):11
2. **Lembke, A.** A downside of electronic health records: How 90 percent of Merced County, California patients became Albanian, *Scope*, the Stanford University School of Medicine blog, October 11, 2012.
3. **Lembke, A.** To reduce use, educate teens on the risks of marijuana and prescription drugs, *Scope*, the Stanford University School of Medicine blog, October 18, 2012.
4. **Lembke, A.** Why doctors prescribe opioids to patients they know are abusing them, *Scope*, the Stanford University School of Medicine blog, October 25, 2012.
5. **Lembke, A.** How to make alcoholics in recovery feel welcome this holiday season, *Scope*, the Stanford University School of Medicine blog, December 10, 2012.
6. **Lembke, A.** The DSM-V Gets it Right. *The Fix*, April 11, 2013.
7. **Lembke, A.** Inside the Mind of an Addiction Medicine Physician, *The Fix*, December 4, 2014.
8. **Lembke, A.** Unmet Expectations: Testifying before Congress on the Opioid Abuse Epidemic, *Scope*, the Stanford University School of Medicine blog, April 29, 2015
9. **Lembke, A.** Ask an Expert. Should I go off Suboxone? If so, how? *The Fix*, April 29, 2015
10. **Lembke, A.** Ask an Expert: Should I Go Through Detox if I'm Not Sure I Want to Be Abstinent? *The Fix*, May 10, 2016
11. **Lembke, A.** Prince, opioids and the rest of us: America needs a massive public education campaign to help people hooked on Percocet and related drugs, *New York Daily News Op-Ed*, May 11, 2016

12. **Lembke, A.** Be sure the check the PDMP before prescribing controlled medications, *Psychiatric News*, June 17, 2016
<http://psychnews.psychiatryonline.org/doi/full/10.1176/appi.pn.2016.pp6b2>
13. **Lembke, A.** The Compassionate Doctor, the Narcissistic Injury, and the Prescription Opioid Epidemic. *The Fix*, Nov 30, 2016 <https://www.thefix.com/compassionate-doctor-narcissistic-injury-and-prescription-opioid-epidemic>
14. **Lembke, A.** Commentary provided in response to Joseph Bernstein’s “Not the Last Word: Viscosupplementation, Opioid Overuse, and the Excesses of Empathy”, *Clin Orthop Relat Res* (2017) 475:2369–2372
15. **Lembke, A.** Purdue Pharma is Done Promoting Opioids: Here’s Why It’s a Big Deal, *Fortune Magazine*, Feb 2018 <http://fortune.com/2018/02/13/purdue-pharma-oxycontin-opioid-crisis/>
16. **Lembke A.** Can medical marijuana replace opioids to relieve cancer pain? *HemOnc Today*. 2018;19(24):13.
17. **Lembke, A., Eyal, N.** *Is Social Media Hijacking our Minds?*, Pairagraph: A hub of discourse between pairs of notable individuals,
<https://www.pairagraph.com/dialogue/efa31e60b1e2498588ddc10d074b494c>
18. Ballanyne, Jane C.; Butler, Judy; Coelho, Paul; Franklin, Gary M.; Fugh Berman, Adriane; Gelfand, Stephen; Johnson, Chris; Juurlink, David; Kolodny, Andrew; **Lembke, Anna**; Orr, Rosemary; Streltzer, Jon; Sullivan, Mark D.; Tauben, David J. Tully, Betts; Von Korff, Michael. Letter from Physicians for Responsible Opioid Prescribing (PROP) to the American Medical Association (AMA) -- RE: AMA’s Opposition to Dose & Duration Guidance for Opioid Prescribing.
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Selected Invited Lectures/Testimony (2015-present)

Regional Audience

1. Feb 2015 *Drug Addiction and the Internet: Justin’s Story*, Psychiatry Grand Rounds, Alta Bates Summit Medical Center, Berkeley, CA
2. Feb 2015 *Pain, Addiction, and the Drug-Seeking Patient: Compassionate Care for a Complex Problem*, Santa Clara Valley Medical Center CME Symposium on Addiction, Santa Clara, CA
3. March 2015 *The Prescription Drug Epidemic: Technology as Both Friend and Foe*, Northern California Psychiatric Society Annual CME Conference, Monterey, CA
4. Sept 2015 *The Prescription Drug Epidemic: Preserving Compassion for the Drug-Seeking*

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Patient, Mills Peninsula Health Services CME Lecture Series, San Mateo, CA

5. Oct 2015 *Addiction Medicine: Managing Prescription Drug Misuse and Addiction, Emerging and Innovative Trends in Psychiatry and Behavioral Health*, Stanford University School of Medicine, Stanford, CA
6. Oct 2015 *The Prescription Drug Epidemic: How Doctors are Complicit, and How We Can Do Better*, Regional Medical Center of San Jose CME Lecture Series, San Jose, CA
7. Dec 2015 *Exploring Dual Diagnosis: What came first, the substance use disorder or the psychiatric disorder, and does it even matter?* Mills Peninsula Health Services CME Lecture Series, San Mateo, CA
8. Jan 2016 *The Prescription Drug Epidemic and the Doctor Patient Relationship*, San Francisco General Hospital Primary Care Grand Rounds, San Francisco, CA
9. March 2016 *Protecting our Developing Youth: Adolescent Addiction, Prevention and Recovery*, Keynote Speaker, Adolescent Counseling Services, East Palo Alto, CA
10. March 2016 *Opioid Therapy for Chronic Non-Cancer Pain*, 2016 Third Annual Addiction Medicine Conference, San Jose Valley Medical Center, San Jose, CA
11. March 2016 *The Prescription Drug Epidemic*, Keynote Speaker, Stanford Annual Adjunct Faculty Retreat, Palo Alto, CA
12. Sept 2016 *Pharmacotherapy for Substance Use Disorders*, Department of Psychiatry Annual CME Conference, Stanford University School of Medicine, Stanford, CA
13. Nov 2016 *Prescription Drug Misuse and the Doctor Patient Relationship*, Psychiatry, San Mateo County Health Systems Grand Rounds, San Mateo, CA
14. March 2017 *The Worst Opioid Epidemic in U.S. History: How did we get here, and how can we get out?* Santa Cruz Health Care Initiative, Santa Cruz, CA
15. March 2017 *The Canary in the Coal Mine: The Prescription Drug Epidemic as a Symptom of a Faltering Health Care System* Valley Care Medical, Pleasanton, CA
16. March 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Northern California Psychiatric Society, Napa Valley, CA
17. April 2017 *Pharmacotherapy for Addictive Disorders*, Alta Bates Grand Rounds, Alta Bates Hospital Berkeley, CA
18. May 2017 *The Worst Opioid Epidemic in U.S. History: How did we get here, and how can we get out?* Stanford Health Matters, Stanford, CA

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19. May 2017 *The Compassionate Doctor, the Suffering Patient, and the Prescription Drug Epidemic*, Central California Alliance for Health (the Alliance), Merced, California
20. May 2017 *The Compassionate Doctor, the Suffering Patient, and the Prescription Drug Epidemic*, Janus of Santa Cruz, Seaside, California
21. June 2017 *Overprescribing in the Elderly: Causes, Risks, and Interventions*, Keynote Speaker at the 17th Annual California Senior Injury Prevention Educational Forum, Oakland, CA
22. Feb 2018 *Is Marijuana a Harm Reduction Strategy?*, Stanford Psychiatry Grand Rounds, Stanford University School of Medicine, Stanford, CA
23. March 2018 *Raising T(w)eens in a Dopamine Saturated World*, Woodside Priory High School, Woodside, CA
24. March 2018 *Raising T(w)eens in a Dopamine Saturated World*, Sacred Heart High School, Menlo Park, CA
25. April 2018 *The Opioid Epidemic: What Doctors and Hospitals Can Do*, California Pacific Medical Center Internal Medicine Grand Rounds, San Francisco, CA
26. April 2018 *Adolescent Substance Abuse: Risk, Resilience, Prevention, and Treatment*, 2018 Adolescent Mental Wellness Conference, sponsored by Stanford University, Santa Clara, CA
27. July 2018 *Understanding the Opioid Crisis at the End of Life*, San Francisco Bay Area Hospice and Palliative Nurses Association, Stanford, CA
28. Aug 2018 *The Opioid Epidemic: How We Got Here, and How to Get Out*, Apple Corporation, Cupertino, CA
29. Oct 2018 *The Pleasure Pain Balance*, Los Altos High School “STEAM Week”, Los Altos, CA
30. Jan 2019 *From Freud to Fentanyl: The Opioid Epidemic as a Symptom of a Faltering Health Care System*, Internal Medicine Grand Rounds, Santa Clara Valley Medical Center, Santa Clara, CA
31. Feb 2019 *Our Other Prescription Drug Problem (Benzodiazepines and How to Taper)*, Internal Medicine Grand Rounds, San Mateo Medical Center, San Mateo, CA
32. July 2019 *Social Media and Device Addiction*, 27th Annual Pediatric Update, Stanford University School of Medicine, Stanford, CA
33. Aug 2019 *Medical Cannabis: Clinical Issues*, 8th Annual Navigating Spine Conference, Stanford University School of Medicine, Stanford, CA

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34. June 2020, *From Freud to Fentanyl: The Opioid Epidemic as a Symptom of our Faltering Health Care System*, Alta Bates Grand Rounds, Berkeley, CA
35. Aug 2020 *Cannabis: A Practical Clinical Approach*, 9th Annual Navigating Spine Conference, Stanford University School of Medicine, Stanford, CA
36. Nov 2020 *Aging and Alcohol: How Much Is Too Much?* Avenidas Town Hall, Palo Alto, CA
37. Jan 2021 *Physicians with Addiction: Why it Happens and How to Help*, Department of Anesthesiology, Stanford Health Care, Kaweah Delta, CA
38. Feb 2021 *The Neuroscience of Addiction*, Recovery Café, San Jose, CA
39. March 2021 *Alcohol Use Disorder: How Much is Too Much?* Sage Eldercare, Bay Area, California
40. March 2021 *Dopamine Nation: Finding Balance in the Age of Indulgence*, The Parent Venture, Menlo Park, CA
41. March 2021 Stanford Healthy Living Class on "The Science of Addiction: What It Is, How It Affects Our Brains, and What We Can Do About It"

National/International Audience

1. Sept 2015 *The Prescription Drug Epidemic: Compassionate Care for a Complex Problem*, Psychiatry Grand Rounds Speaker, Oregon Health Sciences University, Portland, CA
2. Oct 2015 *Chronic Pain and Addiction: The Compassionate Doctor, The Narcissistic Injury, and the Primitive Defense*, California Society of Addiction Medicine, State of the Art Annual Conference, San Francisco, CA
3. Oct 2015 *Prescription Drug Misuse and the Doctor Patient Relationship*, Keynote Speaker, American Correctional Healthcare Services Association, Tailoring Health Care for Inmates, Sacramento, CA
4. March 2016 *Chronic Opioids: Shifting the Paradigm*, Keynote Speaker, Samaritan Center & Health Career and Training Center, Lebanon, OR
5. June 2016 *The Compassionate Doctor, the Drug Seeking Patient, the Narcissistic Injury, and the Primitive Defense*, Keynote Speaker, Cedar Sinai Annual Psychiatric Conference, Los Angeles, CA
6. Sept 2016 *Myths and Facts about Opioids*, DCRx: The DC Center for Rational Prescribing; <http://doh.dc.gov/dcrx>, Washington, DC

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7. Sept 2016 *Getting Patients Off of Opioids*, DCRx: The DC Center for Rational Prescribing; <http://doh.dc.gov/dcrx>, Washington, DC
8. Oct 2016 *State of the Art Treatment for Substance Use Disorders and other Addictions*, Keynote Speaker, 3-part lecture series, Beijing University, #6 Hospital, Beijing, China
9. Jan 2017 *Effective Strategies for the Non-Adherent Buprenorphine Patient: Rational Monitoring and Contingency*, California Society of Addiction Medicine, Treating Addiction in the Primary Care Safety Net, Webinar
10. Feb 2017 *How to safely taper patients off high dose prescription opioids for chronic pain*, Keynote Speaker, California Center for Care Innovations, Treating Addiction in the Primary Care Safety Net, Los Angeles, CA
11. Feb 2017 *The Worst Opioid Epidemic in U.S. History: How did we get here, and how can we get out?* Stanford Parents Weekend Back to School, Stanford, CA
12. Feb 2017 *When Pain Treatment Becomes Addiction Treatment*, American Psychological Association Annual Meeting, San Francisco, CA
13. Feb 2017 *Parallel Crises: The Over and Under Prescription of Opioids*, American Association of Medical Colleges (AAMC) Webinar
14. March 2017 *How Doctors Contributed to the Opioid Epidemic, and What We Can Do to Fix It*, Intermountain Health Care Book Club Speaker for *Drug Dealer, MD*, Intermountain Health Care, Salt Lake City, UT
15. March 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Culture and Politics of Mental Health, Anthropology 1737-1020, Professor Tomas Matza, University of Pittsburg, Pittsburg, PA
16. April 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Stanford TEDx, Stanford, CA
17. April 2017 Invited speaker, 6th Annual Health Technology Forum Innovation Conference: *Common Good!* Stanford University School of Medicine, Stanford, CA
18. April 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Keynote Speaker, 8th Annual Lloyd C. Elam Symposium, Meharry Medical College, Nashville, TN
19. April 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Keynote Speaker, Association of Contextual Behavioral Sciences (ACBS), Chicago, IL

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20. May 2017 *Invisible Forces Driving the Opioid Epidemic: From Disability Reform to Illness Narratives*, Keynote Speaker, OPG 6th Annual Pain Conference Agenda, Ashland, OR
21. May 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Internal Medicine Residency Program Invited Visiting Professor and Grand Rounds Speaker, Johns Hopkins Bayview Medical Center, Baltimore, MD
22. June 2017 *Invisible Forces Driving the Opioid Epidemic: From Disability Reform to Illness Narratives*, Keynote Speaker, PharmedOut Annual Conference, Georgetown University Medical Center, Washington, DC
23. Sept 2017 *The Opioid Epidemic*, Keynote Speaker, Department of Labor West Coast Symposium, San Francisco, CA
24. Sept 2017 *Treating Addiction without Feeding It*, Keynote Speaker, American Correctional Health Services Association (ACHSA) "Modern Challenges in Jails and Prisons", San Jose, CA
25. Sept 2017 *Invisible Forces Driving the Prescription Drug Epidemic: From Disability Reform to Illness Narratives*, Keynote Speaker, The International Benzodiazepine Symposium, Redmond, OR
26. Sept 2017 *Reframing Medical Practice Involving Controlled Substances*, Keynote Speaker, The Association of State and Territorial Health Officials (ASTHO) 2017 Annual Conference, Washington, DC
27. Oct 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Keynote Speaker, The Patient Safety Institute for Mission Health 3rd Annual National Patient Safety Conference – Cultivating a Culture of Safety, Asheville, NC
28. Nov 2017 *The Opioid Epidemic, How We Got Here, and How We Can Get Out*, Keynote Speaker, American Association of Medical Colleges, Learn, Serve, Lead, Boston, MA
29. Nov 2017 *The Opioid Fallout: Lives, Jobs and a Lost Generation*, Bloomberg News Live, The Year Ahead, Bloomberg Headquarters, New York City, NY
30. Nov 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Grand Rounds Speaker, Westchester Medical Center, Westchester, NY
31. Dec 2017 *The Opioid Epidemic: How We Got Here, and How We Can Get Out*, Keynote Speaker, Primary Care and Behavioral Health Integration Summit, Health Quality Partners, San Diego, CA
32. Jan 2018 *How to Survive in a Dopamine Saturated World*, Psychiatry Grand Rounds, Vanderbilt University School of Medicine, Nashville, TN

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33. April 2018 *Drug Dealer, MD*, Keynote Speaker, STAR Trauma Recovery Center, Ohio State University Medical School, Columbus, OH
34. May 2018 *The Opioid Epidemic: What Doctors and Hospitals Can Do*, Alpha Omega Alpha Visiting Professorship, Psychiatry Grand Rounds, University of Kansas School of Medicine, Kansas City, KS
35. May 2018 *Opioids, Pain and Addiction Treatment: Pioneering Change*, Oregon Pain Guidance Annual Conference, Eugene, OR
36. June 2018 *The Opioid Epidemic, How We Got Here and How to Get Out*, Indiana Prosecuting Attorneys Council (IPAC), invited speaker, French Lick, IN
37. June 2018 *What is Addiction and How to Treat It*, Perrin's Opioid Litigation Conference, Dallas, TX
38. Aug 2018 Moderator, *Beyond Nature and Nurture – Social Determinants of Addiction and Health*, California Society of Addiction Medicine State of the Art Annual Conference, San Francisco, CA
39. Aug 2018 *Drug Dealer, MD: The Opioid Crisis*, Apple Corporation Wellness Outreach, Cupertino, CA
40. Sept. 2018 *The Opioid Epidemic: How We Got Here, and How to Get Out*, Public Funds Forum, Laguna Beach, CA
41. Sept 2018 *Drug Dealer, MD: The Opioid Crisis*, Baton Rouge Health District Community Service Talk and Medical Center Grand Rounds, Baton Rouge, LA
42. Sept 2018 *Drug Dealer, MD: The Opioid Crisis*, Montrose Annual CME Conference, Montrose, CO
43. Oct 2018 *The Opioid Epidemic: From Freud to Fentanyl*, Keynote Speaker, PerformRX Pharmacy Benefits Manager Annual Conference, Orlando, FL
44. Oct 2018 *The Opioid Epidemic: How We Got Here, Where We Are Now, and How to Get Out*, Keynote Speaker, Distinguished Lecture Series, Annual Meeting of the American Academy of Psychiatry and the Law (AAPL), Austin, TX
45. Oct 2018 *Drug Dealer MD: The Opioid Epidemic*, Keynote Speaker, Psych Congress, Orlando, FL
46. Dec 2018 *How to Taper Patients Off of Chronic Opioid Therapy*: 69th Annual Refresher Course for Family Physicians, Montreal, Canada

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47. Feb 2019 *The Opioid Epidemic: How We Got Here, Where We Are Now, and How to Get Out*, National Keynote Speaker, Ohio State University Inter-Professional Summit, Columbus, OH
48. Feb 2019 *The Opioid Epidemic: How We Got Here, Where We Are Now, and How to Get Out*, Keynote Speaker, Pain and Addiction Summit, AT&T Conference Center/University of Texas, Austin, TX
49. April 2019 *The Opioid Epidemic: From Freud to Fentanyl*, Keynote, Speaker, Geminus Community Partners Annual Conference, Merrillville, IN
50. April 2019 Invited commentator on *Deaths of Despair* for honorees Princeton Economists Ann Case and Angus Deaton, The 2019 Tanner Lectures on Human Values, Sponsored by the Office of the President and the McCoy Family Center for Ethics in Society, Stanford, CA
51. April 2019 *The Opioid Epidemic: Where We Are Now*, Keynote speaker for the National Council on Alcoholism and Drug Abuse (NCADA) Spring Awards Luncheon, St. Louis, MO
52. May 2019 *The Opioid Epidemic: Where We Are Now*, Faculty presenter Stanford Sierra Camp Womens' Alumni Wellness Retreat, Fallen Leaf Lake, CA
53. May 2019 *The Opioid Epidemic: From Freud to Fentanyl*, The American Psychiatric Association Annual Meeting, San Francisco, CA
54. July 2019 *Rethinking Opioid Tapers, Buprenorphine Induction, and Perioperative Buprenorphine*, Opioid Response Network Texas Grand Rounds National Webinar Series
55. July 2019 *Tapering Guidance for Opioids*, National Academy of Medicine webinar <https://nam.edu/event/webinar-tapering-guidance-for-opioids-existing-best-practices-and-evidence-standards/> ; <https://nam.edu/wp-content/uploads/2019/08/Tapering-webinar-two-pager-FINAL.pdf>.
56. Nov 2019 *Tapering Opioids: Compassionate Care or Punitive Policy*, AMERSA Conference, Boston, MA
57. Dec 2019 *From Freud to Fentanyl: The Opioid Epidemic as a Symptom of our Faltering Health Care System*, Southwestern Gynecologic Assembly 54th Annual Meeting: Patient and Provider at Their Best: Caring for Patients and Yourself, Dallas, TX
58. March 2020 *Dismantling the Addiction Industrial Complex*, 13th Annual Haas Healthcare Conference, "Foresight is 2020," San Francisco, CA
59. Aug 2020 *What's Next in the Opioid Epidemic: How to Taper Long-Term Opioid Therapy*, The Align Conference Evidence in Motion, online conference
60. Oct 2020 *The Opioid Epidemic, An Update ... Plus A Word on Cannabis*, James O. Johnson

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Orthopedic Symposium, The Kaiser Permanente Group, online conference

61. Dec 2020 *Chatham House Webinar: Freedom of Thought and Opinion in the Digital Age*, The Royal Institute of International Affairs Chatham House, 10 St James's Square, London, England
62. Dec 2020 *Benzodiazepines: A Crisis Hidden in Plain Sight*, American Academy of Addiction Psychiatry, San Antonio, TX.
63. Jan 2021 *The Impact of Technology on Mental Health*, Q & A with Microsoft Interns, online panel discussion with Tim Kendall and Jaron Lanier
64. Jan 2021 *Addiction and Technology*, online guest speaker and panelist, University of Toronto Artificial Intelligence Conference, Toronto, CA
65. Feb 2021 *Dopamine Nation: Finding Balance in the Age of Indulgence*, Luxembourg Stanford Alumni Association, Luxembourg
66. Feb 2021 *Social Media: Why It's Addictive and How to Use It in Healthier Ways*, National Association of Pediatric Nurse Practitioners, San Francisco, CA
67. March 2021 *Social Media: Why It's Addictive and How to Use It in Healthier Ways*, The Royal Institute of International Affairs Chatham House, 10 St James's Square, London, England
68. March 2021 *Dopamine Nation: Finding Balance in the Age of Indulgence*, Alpha Omega Alpha Visiting Professorship Grand Rounds, University of Nevada Medical School (Reno)
69. Nov 2021 *Dopamine Nation: Finding Balance in the Age of Indulgence*, for YPO <https://www.ypo.org/who-is-ypo/>, Fort Worth, TX
70. June 2021 *Social Media Addiction: Why It Happens and What To Do About It*, Grand Rounds at Mercy Fitzgerald Hospital, Philadelphia

United States Government Testimony/White House Appearances/Consulting

1. April 2015 Expert testimony for the Congress of the United States, House of Representatives, Committee on Energy and Commerce, Subcommittee on Oversight and Investigations hearing entitled “Combating the Opioid Abuse Epidemic: Professional and Academic Perspectives,” Washington, D.C. <https://democrats-energycommerce.house.gov/committee-activity/hearings/hearing-on-combatting-the-opioid-abuse-epidemic-professional-and>
2. Sept 2015 Expert testimony for the White House Symposium, “Medicine Responds to the Need for Addiction Expertise”, The Office of National Drug Control Policy, The White House, Washington, D.C. <https://obamawhitehouse.archives.gov/the-press-office/2015/09/18/white-house-drug-policy-office-hosts-%E2%80%9Cmedicine-responds->

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3. Sept 2016 Expert testimony for the United States Senate, Committee of Homeland Security and Government Affairs, Permanent Subcommittee on Investigations, on the overuse and overprescribing of prescription opioids, “Combating the Opioid Epidemic: A Review of Anti-Abuse Efforts by Federal Authorities and Private Insurers”, Washington, D.C.
4. Oct 2016 Expert testimony for the White House Symposium, “Academic Medical Centers as Centers of Excellence in Addiction Medicine”, The Office of National Drug Control Policy, The White House, Washington, D.C. <http://www.abms.org/news-events/white-house-symposium-briefing-session-on-addiction/>
5. May 2017 Provided consultation on curbing the opioid epidemic to Nevada’s Office of the Governor
6. May 2017 Provided consultation on curbing the opioid epidemic to Kentucky’s Office of the Governor
7. Sept 2017 Expert Spoken and Written Testimony for the Congress of the United States, House of Representatives, “Addiction Medicine: The Urgent Need for Trained Physicians”, hosted by The Addiction Medicine Foundation and co-sponsored by the Congressional Prescription Drug Abuse Caucus, the Congressional Addiction Treatment and Recovery Caucus, and the Congressional Bipartisan Heroin Task Force <https://www.youtube.com/watch?v=y6kBoQckmHw>
8. Jan 2018 Expert testimony in federal court, Judge Dan Polster presiding, in the multi-district litigation lawsuit against opioid manufacturers and distributors <https://www.law360.com/articles/1008010/inside-the-opioid-mdl-s-big-closed-door-hearing>
9. March 20, 2019 Testimony by Stanford University Professor Anna Lembke to Joint Hearing of Senate and General Assembly Health and Human Services Committees on “Opioids, cannabis, and vaping: Using science to protect public health” State of Rhode Island

Medical Expert Witness (last 5 years)

1. People v. Ingram, Philip Morris (Sup. Ct. of CA, Docket 62-144622), (2018)
2. Federal (MDL) and state (California, New York, Texas, West Virginia, Washington) litigation against opioid manufacturers, distributors, and other defendants (plaintiff side) (January 2018 ongoing)
3. Miner v. Olsen and Lawson (December 2020 ongoing)

Media Appearances (2015-present)

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1. April 2015 *Public Radio International-To the Point*, hosted by Warren Olney, prescription opioid and heroin abuse in America, invited expert.
2. Oct 2015 *OnPoint, National Public Radio*, the prescription opioid epidemic, invited expert
3. March 2016 *Al Jazeera* live programming, the new CDC guidelines on opioid prescribing, invited expert
4. March 2016 *KCBS Radio*, San Francisco, the new CDC guidelines on opioid prescribing, invited expert
5. April 2016 *The Today Show* on NBC, NY, New York, appearance with Mehmet Oz discussing “The Opioid Epidemic”
6. May 2016 *KCBS Radio*, San Francisco, the FDA approves Probuphine, a buprenorphine implant, invited expert
7. Oct 2016 *Opioids: Last Week Tonight with John Oliver* (HBO),
<https://www.youtube.com/watch?v=5pdPrQFjo2o>
8. Nov 2016 *Sirius XM Radio*, invited guest to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It’s So Hard to Stop*
9. Nov 2016 *Wisconsin Public Radio's "Central Time" Show*, invited guest to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It’s So Hard to Stop*
<http://www.wpr.org/connection-between-illicit-drugs-and-doctors>
10. Nov 2016 *The Healthcare Policy Podcast with David Introcaso*, invited podcast to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It’s So Hard to Stop* <http://www.stitcher.com/podcast/david-introcaso-2/the-healthcare-policy-podcast/e/what-explains-the-opioid-epidemic-dr-anna-lembke-discusses-48277528>
11. Nov 2016 *Straight Talk MD with Frank Sweeny* invited podcast to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It’s So Hard to Stop*
<http://straighttalkmd.com/podcast/drug-dealer-md-opioid-epidemic-anna-lembke-md/>
12. Nov 2016 *Conversation on Healthcare Reach MD Radio*, invited guest to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It’s So Hard to Stop*
<http://www.chcradio.com/episode.php?id=360>
13. Nov 2016 *KALW Local Public Radio*, invited guest to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It’s So Hard to Stop*
<http://kalw.org/post/city-visions-how-doctors-fueled-opioid-epidemic#stream/0>
14. Nov 2016 *Forum with Michael Krasny (KQED-FM)* invited panelist to discuss “The Surgeon General’s Report: Facing Addiction in America,”

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<https://ww2.kqed.org/forum/2016/11/28/addiction-is-illness-not-a-moral-failing-says-surgeon-general/>

15. Nov 2016 *Stanford Scope 1:2:1 Podcast with Paul Costello* invited podcast to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop* <http://med.stanford.edu/news/all-news/one-to-one/2016/drug-dealer--md--how-physicians-are-fueling-the-opioid-epidemic.html>
16. Dec 2016 *Straight Talk MD with Frank Sweeny* invited podcast to discuss “The Surgeon General’s Report: Facing Addiction in America,” <https://www.acast.com/straighttalkmd/facing-addiction-in-america-the-surgeon-generals-report>
17. Dec 2016, *NPR Fresh Air with Terry Gross* ‘Drug Dealer, M.D.’: Misunderstandings And Good Intentions Fueled Opioid Epidemic invited interview to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop* <http://www.npr.org/sections/health-shots/2016/12/15/505710073/drug-dealer-md-contentends-that-well-meaning-docs-drove-the-opioid-epidemic>
18. Dec 2016 *The Jimmy Moore Show* invited podcast to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*
19. Feb 2017 *WILK Radio, The Sue Henry Show* invited guest to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*
20. Feb 2017 *Reach, MD* with host John J. Russell, MD invited guest to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop* <https://www.reachmd.com/programs/book-club/drug-dealer-MD-how-doctors-duped-patients-hooked-why-so-hard-stop/8512/>
21. March 2017 *MSNBC with Chris Hayes*, live guest appearance to discuss the opioid epidemic in West Virginia <https://www.youtube.com/watch?v=0Ar30-kDSUQ&sns=em>
22. March 2017 *Stanford Law School Wellness Project Podcast*, with Dr. Joseph Bankman and Dr. Sarah Weinstein, to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop* www.law.stanford.edu/wellnessproject
23. March 2017 *SiriusXM’s Tell Me Everything with John Fugelsang*, invited guest to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*
24. June 2017 *The Texas Standard Radio Show*, invited guest to discuss the FDA decision to ask Endo Pharmaceuticals to withdraw Opana ER from the market <http://www.texasstandard.org/stories/fda-wants-painkiller-favored-by-opioid-abusers-off-the-market/>

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25. June 2017 *NBC Television Sunday Night with Megyn Kelly*, invited expert to discuss marijuana legalization <http://www.nbc.com/sunday-night-with-megyn-kelly/video/sunday-night-with-megyn-kelly/3536915>
26. June 2017 *KCBS Radio in San Francisco* invited guest to discuss the ongoing opioid epidemic
27. July 2017 KPCC's *AirTalk* with host Larry Mantle, live guest appearance to discuss the opioid crisis <http://www.scpr.org/programs/airtalk/2017/07/20/58084/in-the-context-of-the-opioid-crisis-doctors-discus/>
28. July 2017 Jose Calderon *Mindful Psychiatry Live Radio and Podcast*, invited guest to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop* <http://wholebodymentalhealth.libsyn.com/hard-pill-to-swallow-drug-dealer-md-with-dr-anna-lempke-md-7-5-17>
29. Aug 2017 KQED Forum with Michael Krasny Live Radio Broadcast, invited guest to discuss *Rise in High-Risk Drinking a Public Health Crisis, New Study Finds*
30. Aug 2017 MSNBC with Chris Hayes, live guest appearance to discuss President Trump's inaction on the opioid epidemic <http://www.msnbc.com/all-in/watch/donald-trump-has-done-nothing-on-the-opioid-crisis-1032009795986>
31. Sept 2017 KPCC's *AirTalk* with host Larry Mantle, live guest appearance to discuss CVS Pharmacy's announcement it will limit opioid prescriptions to seven days for certain conditions for new patients seeking drugs for pain relief.
<http://www.scpr.org/programs/airtalk/2017/09/22/59288/how-much-would-cvs-s-7-day-limit-on-painkiller-pre/>
32. Oct 2017 BBC Newshour on BBC World Service radio on the opioid epidemic with host James Menendez <http://www.bbc.co.uk/programmes/w172vghc8jkr3g>
33. Oct 2017 NBCUniversal live in the studio with Dr. John Torres, *One Nation Overdosed: Doctors Speak Out* <http://qlnk.io/ql/59f0f15be4b0945e5d8ff73f>
34. Oct 2017 KPIX 5 CBS San Francisco Trump declares the opioid epidemic a public health emergency <http://sanfrancisco.cbslocal.com/video/3752604-critics-say-trumps-opioid-announcement-doesnt-go-far-enough/>
35. Oct 2017 KPIX 5 CBS San Francisco commentator on bay area parents using marijuana <http://sanfrancisco.cbslocal.com/2017/11/04/marin-mom-marijuana-makes-her-better-parent/>
36. Jan 2018 KQED with Brian Watt on "smartphone addiction"
<https://soundcloud.com/kqed/investors-urge-apple-to-take-action-to-curb-digital-device-overuse-among-children>

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37. Feb 2018 Sirius/XM radio with Clare Marie Gauthier, Co-Host, Dave Nemo Weekends, RadioNemo of North America, on the opioid epidemic and *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*
38. Feb 2018 KQED News radio, report on Purdue Pharma's decision to stop marketing opioids directly to doctors
39. Feb 2018 NPR Smartphone Detox, How to Power Down in a Wired World
<https://www.npr.org/sections/health-shots/2018/02/12/584389201/smartphone-detox-how-to-power-down-in-a-wired-world>
40. March 2018 Sirius/XM Radio with Clare Marie Gauthier, Co-Host, Dave Nemo Weekends, RadioNemo of North America, on addiction treatment
41. March 2018 Sirius/XM Radio "Doctor Radio", on the silent benzodiazepine epidemic
42. March 2018 Sirius XM Radio: POTUS Channel 124, "Steele & Ungar", on new Center for Medicare and Medicaid Services regulations to restrict opioid prescribing
43. March 2018 KPCC's AirTalk with host Larry Mantle, live guest appearance to discuss new Center for Medicare and Medicaid Services regulations to restrict opioid prescribing
44. March 2018 Science VS. with Rose Rimler, "Opioids: Kicking America's Addiction"
<https://www.gimletmedia.com/science-vs/opioids-kicking-americas-addiction#episode-player>
45. April 2018 KQED Forum with Michael Krasny, Medical Community Divided On Medicare's Policy to Shorten High-Dose Opioid Prescriptions,
<https://www.kqed.org/forum/2010101864587/medical-community-divided-on-medicare-policy-to-shorten-high-dose-opioid-prescriptions>
46. May 2018 Radio Health Journal with Reed Pence: The Opioid Epidemic,
http://mediatracks.com/shows/RHJ_18-17.mp3
47. May 2018 Straight Talk MD: Health | Medicine | Healthcare Policy | Health Education | Anesthesiology, The Cannabis Conversations: Part II with Anna Lembke MD
<http://straighttalkmd.com/podcast/the-cannabis-conversations-part-ii-with-anna-lembke-md/>
48. June 2018 The Future of Everything with Russ Altman (Stanford Radio), 06/18/18. In a recent segment on Stanford Radio, Russ Altman discussed the rise of the opioid epidemic in the United States with Anna Lembke. <https://soundcloud.com/user-458541487/facing-addiction-with-guest-anna-lembke>
49. July 2018 NBC News with Dr. John Torres to discuss benzodiazepines https://www.nbcnews.com/nightly-news/video/is-anti-anxiety-medication-the-next-u-s-drug-crisis-1287215683720?cid=eml_on-site

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50. Oct 2018 NOVA/PBS documentary ADDICTION, Produced, Directed and Written by Sarah Holt, Co-producer Julie Crawford <http://www.holtproductions.org>; <http://www.pbs.org/wgbh/nova/body/addiction.html>
51. March 11, 2019 Spectrum News In Focus, What's Causing the Opioid Crisis, with Renee Eng, <https://spectruminfocus.com/section/in-focus/in-focus/2019/03/11/in-focus--what-s-causing-the-opioid-crisis#>
52. April 29, 2019 KALW City Visions, California's drug rehabilitation industry, <https://www.kalw.org/post/city-visions-reforming-californias-drug-rehabilitation-industry#stream/0>
53. May 20, 2019 Groundless Ground podcast with Lisa Dale Miller, Chronic Pain, Dual-Diagnosis and Addiction Treatment, <https://groundlessground.com/episodes/anna-lembke-chronic-pain-dual-diagnosis-and-addiction-treatment>
54. June 24, 2019 KCBS News Radio San Francisco 10 Q's w/Stan & Susan, to discuss rising rates of fentanyl overdose in San Francisco <https://kcbssradio.radio.com/blogs/margie-shafer/fentanyl-becomes-san-francis>
55. July 18, 2019 Russian Television News (RT International) "The Opioid Epidemic in the United States: Where Are We Now?" <https://www.youtube.com/watch?v=KP-Vn2d6LWk>
56. Aug 26, 2019 Russian Television News (RT International) on the Oklahoma vs Johnson & Johnson opioid litigation <https://youtu.be/sNKrMYIrPtE>
57. Aug 29, 2019 Monocle 24 Radio in London on the opioid crisis in follow up to the outcome of the Oklahoma vs Johnson & Johnson opioid litigation
58. Sept 2019 American Journal of Psychiatry Residents' Journal podcast series <http://ajpresidentsjournal.apapublishing.libsynpro.com>
59. Sept 2019 *The Voice of Medicine* podcast, m.hulik@radiolutions.com
60. Oct 2019 *This is Life with Lisa Ling*, Benzodiazepines, <https://www.cnn.com/2019/10/04/health/benzodiazepines-this-is-life-with-lisa-ling/index.html> ; <https://itunes.apple.com/us/tv-season/this-is-life-with-lisa-ling-season-6/id1480545936>
61. Oct 2019 *Straight Talk with Frank Sweeny*, Benzodiazepines, <https://podcasts.apple.com/us/podcast/straight-talk-md-health-medicine-healthcare-policy/id1060256849#episodeGuid=78d97afe7ea14dac8261193a2aa3d69> ; <https://open.spotify.com/episode/ljrtfq60dmraRnzTtsUNeb?si=jO2RZqjDTM-c1VJUVsWcuw>
62. Dec 2019 CBSN Bay Area, 12/09/19 *Medical Monday: How to avoid overindulging in*

alcohol during the holiday season and setting healthy drinking limits

<https://sanfrancisco.cbslocal.com/live/cbsn-bay-area/video/3439448-20191209162159-medical-mondays-dr-anna-lembke-addiction-recovery-relapse-triggers/>

63. Feb 2020 Netflix's "The Pharmacist" explores how pill mill doctors fanned the flames of the country's opioid epidemic by flagrantly overprescribing three particular drugs. Anna Lembke, associate professor of psychiatry and behavioral sciences, is quoted in this piece. <https://www.oxygen.com/true-crime-buzz/oxycotin-soma-xanax-the-holy-trinity-from-the-pharmacist-explained>
64. Feb 2020 Anna Lembke appeared on the Netflix documentary series *The Pharmacist*. <https://www.netflix.com/title/81002576>
65. Feb 2020 *What Makes Up Your Mind: Opioids And Addiction with Dr. Anna Lembke*, Stanford University Department of Psychiatry Podcast, <https://m.soundcloud.com/stanfordpsy/february2020/s-kBmxv>
66. Feb 2020 Sirius XM Doctor Radio, invited guest to discuss benzodiazepines, Scott.Uhing@SiriusXM.com
67. Apr 2020 *Mental Health During Quarantine*, Doc to Doc with Dr. John Torres, Medical Correspondent NBC News and MSNBC, Facebook Live, <https://www.facebook.com/NBCNews/videos/doc-to-doc-coronavirus-conversation-with-dr-anna-lembke/280171329668121/>
68. Jul 2020 *The Therapy Show* with Dr. Bridget Nash, <https://www.therapyshow.com/podcasts/episode/2986f561/drug-dealer-md-author-dr-anna-lembke-discusses-the-latest-treatments>
69. Aug 2020 *How is the Pandemic Affecting People Struggling with Addiction*, Stanford Medicine Scope Interview with Paul Costello <https://scopeblog.stanford.edu/2020/08/11/how-the-pandemic-is-affecting-people-struggling-with-addiction/>
70. Aug 2020 *How the Pandemic is Affecting People Struggling with Addiction*, Stanford Medicine's Paul Costello speaks with Anna Lembke, MD, Associate Professor of psychiatry and behavioral sciences, for a 1:2:1 podcast about the impact of the pandemic on people with drug and alcohol addiction. <https://scopeblog.stanford.edu/2020/08/11/how-the-pandemic-is-affecting-people-struggling-with-addiction/>
71. Sept 2020 *COVID-19 and Mental Health with Anna Lembke MD* from Straight Talk MD with Frank Sweeny on Apple Podcasts <https://podcasts.apple.com/us/podcast/straight-talk-md/id1060256849?i=1000489628559>
72. Sept 2020 Anna Lembke appeared on the [Netflix](#) documentary *The Social Dilemma*, explaining that "social media is a drug" which exploits the brain's evolutionary need for

interpersonal connection. <https://www.thesocialdilemma.com/reclaim-your-screen-time/>

73. Sept 2020 *Officers, tow truck driver released from hospital after Fentanyl exposure scare on Golden Gate Bridge*. Dr. Anna Lembke was interviewed regarding fentanyl exposure. <https://abc7news.com/chp-golden-gate-officers-fentanyl-exposure-bridge-crash-sf-car-crash/6421359/>
74. Oct 2020 *Anna Lembke – Episode 55, Rallen’s Rant* <https://soundcloud.com/richie-allen-3/anna-lembke-episode-55>
75. Nov 2020 *Our Social Dilemma: My Conversation with Dr. Anna Lembke* from 20 Minutes with Bronwyn <https://podcasts.podinstall.com/twentyminuteswithbronwyn-20-minutes-bronwyn/202011031100-our-social-dilemma-my-conversation-dr-anna-lembke.html>
76. November 2020 *The Social Dilemma of a Nation Addicted to Dopamine (ft. Dr. Anna Lembke)* from Designed to Heal. <https://podcasts.apple.com/us/podcast/designed-to-heal/id1479146995>
77. Dec 2020 *Dr Anna Lembke - Addiction and Social Media, Woven Experiences* by Marissa Monnig <https://anchor.fm/marissa-monnig/episodes/Dr-Anna-Lembke---Addiction-and-Social-Media-en7kma>
78. Jan 2021 *The Social Dilemma: Preconceived with Zale Mednick* (Apple Podcasts) <https://link.chtbl.com/FYGb94jM>
79. Jan 2021 *PharmedOut at Georgetown University Panel Discussion w/ Dr. Anna Lembke* <https://www.youtube.com/watch?v=iCaF2JSVhdg&t=6s>
80. Feb 2021 *The “Addict” in All of Us: The Surprising Places Where Addiction Exists*, Dr. Anna Lembke, MD, *The Bottom Line Advocate* With Sarah Hiner <https://bottomlineinc.com/health/addiction/the-addict-in-all-of-us-the-surprising-places-where-addiction-exists-sarah-hiner-talks-to-addiction-specialist-anna-lembke-md>
81. Feb 2021 HBO Panel regarding the documentary *The Crime of the Century* on the opioid crisis
82. March 2021 National Society of High School Scholars Panel with Jeff Orlowski and Tim Kendall on *The Social Dilemma* <https://www.nshss.org/events/past-webinars/>
83. March 2021 *Insight on the Opioid Crisis: An Interview with Dr. Anna Lembke, The Power of the Patient Project* <https://www.youtube.com/watch?v=TtMv6yNl4Uo&t=60s>

Lembke Report

Confidential — Subject to Protective Order

Anna Lembke, M.D. Report

EXHIBIT B

List of Materials Considered

DR. ANNA LEMBKE MATERIALS CONSIDERED

1. 22 Tex. Admin. Code § 170.3 (Amended 2020)
2. 84(R) SB 1462 - TX Opioid Agonist Legislation
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All Expert Witness reports and supplements from MDL 2804 served on March 25, 2019 and May 10, 2019 as well as materials identified within.

All Expert Witness reports from the NY Opioid Litigation 400000/2017 served on December 19, 2019 and February 3rd, 2020 as well as materials identified within.

All Expert Witness reports from Cabell County Commission and City of Huntington, West Virginia, (The Cabell Huntington Community) v. AmerisourceBergen Drug Corporation, Cardinal Health, Inc., and McKesson Corporation served on August 3, 2020 as well as materials identified within.

Lembke Report

Confidential — Subject to Protective Order

Anna Lembke, M.D. Report

EXHIBIT C

Statement of Compensation Rate

Lembke Report

Confidential — Subject to Protective Order

Anna Lembke, M.D.
Stanford University School of Medicine
Department of Psychiatry and Behavioral Sciences

Expert Witness Fee Schedule: *Case No. 18-op-45032 and*

Work	Details	Fee
Preliminary Work	Telephone conferences, record review, report writing, and travel	\$500 per hour
Court Work	Court appearances and depositions	\$800 per hour
Expenses	Travel and other reasonable out-of-pocket expenses	Reimbursement

Lembke Report

Confidential — Subject to Protective Order

Anna Lembke, M.D. Report

EXHIBIT D

Prior Testimony

Lembke Report

Confidential — Subject to Protective Order

Anna Lembke, M.D.
Stanford University School of Medicine
Department of Psychiatry and Behavioral Sciences

Prior Testimony

1. *People v. Philip Morris Ingram*, (Cal. Super. Ct., Docket 62-144622)
2. *National Prescription Opiate Litigation*, MDL No. 2804 (N.D. Ohio, Case 1:17-md-2804)
3. *In Re Opioid Litigation*, (Suffolk County, New York Supreme Court, Index No. 400000/2017), relating to Case Nos. County of Suffolk, 400001/2017; County of Nassau, 400008/2017; and New York State, 400016/2018
4. *Cabell County Commission and City of Huntington, West Virginia, (The Cabell Huntington Community) v. AmerisourceBergen Drug Corporation, Cardinal Health, Inc., and McKesson Corporation*, No. 1:17-op-45053-DAP and No. 1:17-op-45054
5. *People of the State of California v. Purdue Pharma, L.P.*, et al., No. 30-2014-00725287-CU-BT-CXC
6. *Miner v. Olsen, et al.* (arbitration)

DR. ANNA LEMBKE

CT3 SUPPLEMENTAL MATERIALS CONSIDERED LIST

1. Appendix 14 to the Second Supplemental Expert Report of Craig McCann. *The County of Lake, Ohio and The County of Trumbull, Ohio v. Purdue Pharma, LP, et al.*, (Case No. 18-op-45032; Case No. 1:18-op-45079). May 19, 2021
2. Deposition of C. Matthew Hight, *In Re: Texas Opioid Litig.*, No. 18-0358 (Supreme Court of Texas), May 4, 2021
3. Deposition Transcript of Christopher Hepp, *People of the State of California v. Purdue Pharma, L.P., et al.*, No. 30-2014-00725287-CU-BT-CXC, February 11, 2020
4. Deposition Transcript of Patsy Little. *In Re: National Prescription Opiate Litigation* (MDL No. 2804). December 14, 2018.
5. Deposition Transcript of Stephen Said, *In Re: National Prescription Opiate Litigation* (MDL No. 2804). December 12, 2018
6. Expert Report of Carmen Catizone. *The County of Lake, Ohio and The County of Trumbull, Ohio v. Purdue Pharma, LP, et al.*, (Case No. 18-op-45032; Case No. 1:18-op-45079). April 16, 2021
7. Expert Report of James Rafalski. *The County of Lake, Ohio and The County of Trumbull, Ohio v. Purdue Pharma, LP, et al.*, (Case No. 18-op-45032; Case No. 1:18-op-45079). April 16, 2021
8. Expert Report of Lacey Keller. Tables 2 and 4 (IQVIA Xponent®: Dallas County, 1997-2017). *County of Dallas v. Johnson & Johnson, et al.* No. 3:18-cv-00426-M and Cause No. DC-18-00290
9. Gryphon Strategies, Dosage Units and MMEs Shipped to Dallas County. (IQVIA Xponent®: Dallas County, 1997-2017) (April 29, 2021).
10. NIDA. Opioid Overdose Crisis. March 11, 2011. Available at: drugabuse.gov/drugtopics/opioids/opioid-overdose-crisis
11. Second Supplemental Expert Report of Craig McCann. *The County of Lake, Ohio and The County of Trumbull, Ohio v. Purdue Pharma, LP, et al.*, (Case No. 18-op-45032; Case No. 1:18-op-45079). May 19, 2021
12. Supplemental Expert Report of Carmen Catizone. *The County of Lake, Ohio and The County of Trumbull, Ohio v. Purdue Pharma, LP, et al.*, (Case No. 18-op-45032; Case No. 1:18-op-45079). May 19, 2021

DR. ANNA LEMBKE

CT3 SUPPLEMENTAL MATERIALS CONSIDERED LIST

13. Tardif, H., Hayes, C., & Allingham, S. F. (2021). Opioid cessation is associated with reduced pain and improved function in people attending specialist chronic pain services. *The Medical Journal of Australia*.
14. Ung C, Yonekawa Y, Waljee JF, Gunaseelan V, Lai Y, Woodward MA, Persistent Opioid Use After Ophthalmic Surgery in Opioid-Naive Patients and Associated Risk Factors, *Ophthalmology* (2021), doi: <https://doi.org/10.1016/j.optha.2021.04.021>
15. Wilson JD, *et al.* Trajectories of Opioid Use Following First Opioid Prescription in Opioid-Naive Youths and Young Adults. *JAMA Network Open* 4.4 (2021): e214552-e214552.

DR. ANNA LEMBKE

CT3 SUPPLEMENTAL MATERIALS CONSIDERED LIST

BATES STAMPED DOCUMENTS

1. ALLERGAN_MDL_00396747
2. ALLERGAN_MDL_01116687
3. ALLERGAN_MDL_01402098
4. ALLERGAN_MDL_01466324
5. PLT-02U0182F
6. PLTF_2804_000003844
7. PP00532

This supplemental list includes all documents provided to Dr. Lembke since April 16, 2021.